Cognitive Brain Research Unit
Department of Psychology and Logopedics
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Functional and structural correlates of dyslexia and reading-relevant skills in the brain: Evidence from newborns and adults

Anja Thiede

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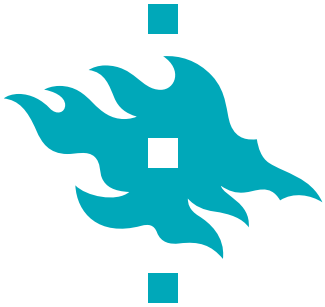

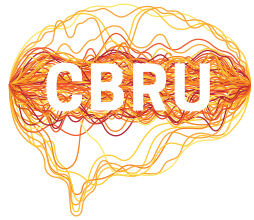

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Cover picture by Caroline Moinel

ISBN 978-951-51-6693-7 (paperback)
ISBN 978-951-51-6694-4 (PDF)
Helsinki 2020
Unigrafia

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Abstract

Developmental dyslexia is at the low end of a spectrum in reading and writing abilities, and may arise despite normal intelligence and education. It often is accompanied by difficulties in domains important for reading, such as phonological processing and verbal working memory. Neural impairments in speech processing are evident in the majority of dyslexic individuals and could be linked to phonological and temporal sampling problems.

This thesis integrates four studies for which neuropsychological assessments, magnetoencephalography (MEG), electroencephalography (EEG), and magnetic resonance imaging (MRI) were conducted. The first study examined the influence of familial dyslexia risk on neural speech-sound discrimination in newborn infants (Study I). The second and third study investigated neural processing of speech-sound changes (Study II) and natural speech (Study III) in adult dyslexic and typical readers. The fourth study analyzed anatomical brain abnormalities in dyslexia (Study IV). In addition, the associations of neural measures to reading and related phonological-processing and working-memory skills were investigated (Studies II–IV).

The main findings of this thesis were neural speech-processing impairments in newborns at risk of and adults with dyslexia, neuroanatomical abnormalities in adults with dyslexia, and links between the neural measures and skills relevant for reading. Specifically, newborns at risk of dyslexia compared to a group of low risk showed atypical neural speech discrimination responses that may be precursors of phonological deficits in dyslexia (Study I). However, neuromagnetic discrimination responses elicited by the same speech-sound changes suggested no abnormalities in adults with dyslexia, yet, the responses were associated with reading and working memory functions (Study II). Inter-subject correlation (ISC) to natural speech was weaker between dyslexic than typically-reading adults in delta- and high gamma-frequency bands, and stronger in the theta, beta, and low gamma bands, possibly reflecting temporal sampling deficits of natural speech fea-

tures (Study III). The ISC strength was related to all three reading-relevant skills of interest. Structural abnormalities were observed in dyslexic adults as decreases in grey- and white-matter volumes in temporal, frontal, and subcortical structures important for reading (Study IV). Furthermore, grey- and white-matter volumes were associated with reading and working memory functions. Taken together, this thesis illuminates neural speech processing deficits in dyslexia and its risk at birth and pinpoints associations between reading skills and neurofunctional and -anatomical measures.

Tiivistelmä

Lukivaikeus on luku- ja kirjoitustaitojen jatkumon matala ääripää, jota ilmenee normaalista älykkyydestä ja koulutuksesta huolimatta. Usein lukivaikeuden ohella esiintyy vaikeuksia muilla lukemiselle tärkeillä osa-alueilla, kuten fonologisessa prosessoinnissa ja kielellisessä työmuistissa. Suurimmalla osalla lukivaikeudesta kärsiviä voidaan todeta puheen hermostollisen käsittelyn häiriöitä, joita on selitetty fonologisen (engl. phonological deficit theory) tai ajallisen käsittelyn (engl. temporal sampling deficit theory) puutteilla.

Tämä väitöskirja koostuu neljästä osajulkaisusta, joita varten tehtiin neuropsykologisia arviointeja, magnetoenkefalografia- (MEG) ja elektroenkefalografiamittauksia (EEG) sekä aivojen rakenteellinen magneettikuvaus (MRI). Ensimmäisessä tutkimuksessa selvitettiin perinnöllisen lukivaikeusriskin vaikutusta puheäänten hermostolliseen erottelutarkkuuteen vastasyntyneillä (Tutkimus I). Toisessa ja kolmannessa tutkimuksessa tarkasteltiin puheäänimuutosten (Tutkimus II) ja luonnollisen puheen (Tutkimus III) hermostollista käsittelyä lukivaikeudesta kärsivillä ja tyypillisesti lukevilla aikuisilla. Neljännessä tutkimuksessa analysoitiin aivojen rakenteellisia poikkeavuuksia lukivaikeudessa (Tutkimus IV). Lisäksi tutkittiin käytettyjen hermostollisten mittarien yhteyksiä lukemiseen ja siihen liittyviin fonologisen prosessoinnin ja työmuistin taitoihin (Tutkimukset II–IV).

Väitöskirjan päälöydöksenä olivat puheen hermostollisen käsittelyn vaikeudet riskiryhmän vastasyntyneillä sekä lukivaikeudesta kärsivillä aikuisilla, aivorakenteen poikkeavuudet lukivaikeudesta kärsivillä aikuisilla ja yhteydet näiden hermostollisten mittarien ja lukemiselle tärkeiden taitojen välillä. Vastasyntyneillä, joilla oli lukivaikeusriski, ilmeni matalan riskin ryhmään verrattuna epätyypillisiä puheäänten erotteluvasteita, jotka saattavat edeltää fonologista häiriötä lukivaikeudessa (Tutkimus I). Samojen puheäänimuutosten aiheuttamat neuromagneettiset erotteluvasteet eivät viitanneet poikkeamiin aikuisilla, joilla oli lukivaikeus, mutta vasteet olivat kuitenkin

yhteydessä lukutaitoon ja työmuistitoimintoihin (Tutkimus II). Aivojen hermosoluryhmien synkronoituminen luonnolliseen puheeseen oli heikompaa lukivaikeuksisten kuin tyypillisesti lukevien aikuisten välillä delta- ja korkeilla gammataajuuskaistoilla ja voimakkaampaa teeta-, beeta- ja matalilla gammakaistoilla, mikä saattaa heijastaa luonnollisen puheen piirteiden käsittelyn häiriöitä (engl. temporal sampling deficits; Tutkimus III). Aivojen hermosoluryhmien synkronoitumisen vahvuus liittyi kaikkiin kolmeen tutkittuun lukemiselle tärkeään taitoon. Aikuisilla, joilla oli lukivaikeus, havaittiin harmaan ja valkean aineen pienentyneitä tilavuuksia lukemisen kannalta tärkeillä alueilla ohimolohkolla, otsalohkolla sekä aivokuoren alaisissa rakenteissa (Tutkimus IV). Lisäksi harmaan ja valkean aineen tilavuudet olivat yhteydessä lukutaitoon ja työmuistitoimintoihin. Kokonaisuutena tämä väitöskirja valottaa puheen hermostollisen käsittelyn häiriöitä lukivaikeudessa ja sen riskissä vastasyntyneillä sekä tuo esiin yhteyksiä lukutaitojen ja toiminnallisten ja rakenteellisten hermostollisten mittarien välillä.

Acknowledgements

A dissertation is not done by one person alone. I want to thank everyone who was involved in this intensive learning process for their support.

This thesis has been conducted at the Cognitive Brain Research Unit (CBRU) at the Medical Faculty of the University of Helsinki. Data were collected at CBRU, Jorvi Hospital and BioMag Laboratory of the Helsinki University Hospital, the University of Jyväskylä, and AMI centre of Aalto University.

First and foremost I want to thank my supervisors Prof. Teija Kujala and Dr. Paula Virtala. Teija, thank you for this opportunity to work on a fascinating topic in an excellent research group, for guiding me along all stages of the process with patience, and for giving me the advice I needed along the way. I appreciate your honesty, efficiency, and scientific rigor. Paula, I am proud to be the very first PhD student you have supervised. Thank you for your hands-on guidance, for helping me to think more critically in the scientific world, and for always being approachable for scientific and other conversations in life. I admire your ability to communicate to the point and to ask the tricky questions. Thank you both for your invaluable support and for being an excellent supervising team that helped me to grow as a researcher!

Thank you for our collaboration Iina Ala-Kurikka, Dr. Eino Partanen, Prof. Minna Huotilainen, Dr. Kaija Mikkola, Prof. Paavo H.T. Leppänen, Prof. Lauri Parkkonen, Prof. Marja Laasonen, Dr. Jyrki Mäkelä, Dr. Enrico Glerean, Peter Palo-oja, Dr. Jussi Numminen, and Dr. Aleksi Sihvonen. You have helped along various stages of the projects with your expertise. Your input in planning and analysis stages, as well as comments on my manuscripts were invaluable, and you were always open for my questions. Lauri, you have been a great mentor from the start of my research career. I admire your ability to explain very complicated and technical details in an easy-to-understand manner. Your contributions to several stages of my projects, especially your methodological advice and approachability for my

questions about small details, have brought me a long way. Special thanks go to Enrico for your hands-on coding advice on the more complicated matters and your encouragement along the way. Thank you Eino for sharing research interests, for related discussions on sometimes tricky matters, and for shedding some light to the mysterious world of infant EEG analysis. Thank you Aleksi for being such a lively spirit, for your excitement about science, and for being reliable and extremely efficient and supportive especially during the final stages of my thesis writing. Marja, thank you for your great help in regard to the neuropsychological tests related to reading skills and dyslexia. Jyrki, thank you for enabling me to carry out MEG measurements at BioMag and for being quick and efficient in organizational and manuscript matters. Iina and Peter, thank you for deciding to work together with me on these projects as follow-ups of your Master's theses. Minna, Kaija, and Paavo, I thank you for contributing with your expertise on infant EEG and dyslexia risk, and for your comments and support around the process of my first scientific publication. Thank you Jussi for agreeing to contribute with your radiological expertise to the MRI-related aspects of my thesis.

It has been fantastic to work with so skilled and responsible team members in the *lukivauva* team. Paula, Sanna, Iina, Oona, Peter, Eino, Linda, Irina, Eliisa, Anastasia, Taru, Tuomas, Teemu, Heidi, Laila, Maaria, Elisa, Ella, you were and are the best team members to have, always open to help and listen, or simply enjoying lunch or coffee breaks together. I am particularly thankful for your patience when I finally decided to speak Finnish with you, and for being encouraging and helpful with that ever since. Special thanks go to Oona, Peter, Irina, Eliisa, Taru, and Tuomas for their help with the MEG and neuropsychological test data collection. Thank you to all our project assistants who have made things run smoothly behind the scenes and for being open for special types of requests.

Having a welcoming atmosphere at CBRU right from the start has made it very easy to feel part of the 'big family'. Thank you's for that go to my current and former colleagues Research Director Dr. Mari Tervaniemi, Piia Turunen, Katja Junttila, Dr. Soila Kuuluvainen, Victória Balla, Linda Kalaheimo-Lönnqvist, Peixin Nie, Dr. Lilli Kimppa, Laura Hedlund, Dr. Suzanne Hut, and Dr. Marina Kliuchko. Especially the 'Exchange club'

has given me the opportunity to learn about and teach varied interesting topics, to exchange experiences and also during stressful times provided moments to laugh together and have a chat. Thank you for your peer support!

Special thanks go to laboratory engineer Tommi Makkonen. You have provided excellent technical help and made my very specific coding wishes reality, always accompanied with a smile and a small chat. Thank you to the highly proficient research nurses Tarja Ilkka and Svetlana Permi for the collection of many, many infant EEG datasets, as well as to radiographer Marita Kattelus for your help with the adult MRI measurements.

I want to thank Prof. Laurel Trainor for so warmly welcoming me to her research group at McMaster University in Canada for a visit in 2016–2017. You enabled me to strive in a different research environment, to learn more about infant EEG, and were contagious with your excitement about science and your ambitious projects and plans. Thank you for being so active and open-minded Dr. Haley Kragness, Dr. Andrew Chang, Prof. Laura Cirelli, Elaine Whiskin, and Susan Marsh-Rollo. With you, I very much enjoyed my time in Hamilton.

With the support of my writing group, scientific writing has gotten easier and more fluent for me, and I have learned a lot during our gatherings and exchanges. Thank you Milla, Maarit, Sailaitha, and Anna for great times in Tvärminne and beyond!

I want to thank my supervisors for allocating part of their project resources to my research and international congress activities. I am also grateful to the University of Helsinki Research Foundation, Arvo and Lea Ylppö Foundation, the Erasmus Mundus Auditory Cognitive Neuroscience Network, and the University of Helsinki MRI measurement fund for supporting my research activities and international mobility.

I thank the two expert reviewers of this thesis, Prof. Riitta Salmelin and Dr. Stefan Elmer and the reviewers of the four articles included in this thesis. Thank you, Prof. Jarmo Hämäläinen for agreeing to act as the opponent of my thesis. I am looking forward to an interesting discussion.

To my friends: I am such a lucky person to have you in my life. Sabrina, Anna, Salla, Marlen, Anna-Lisa, Stephan, Lur, Romy, Wencke, Annalice, Anne, Kerstin, Maja, Enrico, Anu, Ben, Caro, Evisa, Ferdi, David, Carola, Maël, Elena, Luiza, Kike, Jens, Nora, Sakari, I appreciate every small and big moment that we spend together. You remind me of the priorities in life, and are there for me no matter what. I especially thank you for sharing my joy of traveling, for reminding me that long distances can make bonds even stronger, for fun game nights, exploring the beauties of nature, thoughtful book club discussions, active and relaxing Mökki trips, the best parties, and other countless joyful experiences. I am looking forward to every new moment that we will share in the future! Special thanks go to Dr. Benjamin Finley for proofreading my thesis, and to Caroline Moinel for designing a beautiful cover illustration.

Suurkiitos Riikka ja Valentin Nikoloville, että toivotitte minut tervetulleeksi perheeseenne ja monista nautinnollisista ja hauskoista hetkistä.

Ein besonderer Dank geht an meine Familie, Heike, Maik und Felix Thiede. Ihr habt die entscheidenden Weichen gestellt, die mich zu dem Menschen gemacht haben, der ich heute bin. Eure Zuversicht, Unterstützung in jeglicher Hinsicht, Reiselustigkeit, Tatendrang, und ein kleines Körnchen Verrücktheit gepaart mit Witz sind genau die Kombination, auf die ich mich jedes Mal freue, wenn wir uns sehen. Sie gibt mir die Motivation und Stärke meine Ziele zu verfolgen und Träume zu verwirklichen. Danke, dass ihr immer für mich da seid!

Antonio, you have been my anchor and by my side since the beginning of this journey. Thank you for going through all the ups and downs with me, for listening, for your endless support, and for making me laugh so often. I am grateful for everything we share and your love and support mean the world to me.

Helsinki, June 2020
Anja Thiede

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List of original publications

This thesis is based on the following publications:

Study I **Anja Thiede**, Paula Virtala, Iina Ala-Kurikka, Eino Partanen, Minna Huotilainen, Kaija Mikkola, Paavo H.T. Leppänen, Teija Kujala (2019). An extensive pattern of atypical neural speech-sound discrimination in newborns at risk of dyslexia. *Clin. Neurophysiol.* 130, 634–646. doi:10.1016/j.clinph.2019.01.019

Study II **Anja Thiede**, Lauri Parkkonen, Paula Virtala, Marja Laasonen, Jyrki Mäkelä, Teija Kujala (2020). Neuromagnetic speech discrimination responses are associated with reading-related skills in dyslexic and typical readers. *Heliyon.* 6(8), e04619. doi:10.1016/j.heliyon.2020.e04619

Study III **Anja Thiede**, Enrico Glerean, Teija Kujala, Lauri Parkkonen (2020). Atypical MEG inter-subject correlation during listening to continuous natural speech in dyslexia. *NeuroImage.* 216, 116799. doi:10.1016/j.neuroimage.2020.116799

Study IV Teija Kujala, **Anja Thiede**, Peter Palo-oja, Paula Virtala, Marja Laasonen, Jussi Numminen, Aleksi Sihvonen (2020). Neural structures associated with reading and their anatomical abnormalities in dyslexia: a whole-brain analysis. Submitted. *bioRxiv.* 2020.03.27.011577. doi:10.1101/2020.03.27.011577

This thesis contains unpublished material and published material has been reprinted with permission.

Contributions

Study I	The author of the dissertation was involved in recruitment, analyzed the data, prepared the figures and tables for the manuscript, and wrote the first version of the manuscript.
Study II	The author was involved in the planning, recruitment and data collection, analyzed the data, prepared the figures and tables for the manuscript, and wrote the first version of the manuscript.
Study III	The author planned the study, was involved in the recruitment and data collection, analyzed the data, prepared the figures and tables for the manuscript, and wrote the first version of the manuscript.
Study IV	The author was involved in the planning, recruitment and data collection, prepared tables for the manuscript, and wrote parts of, reviewed and edited the manuscript.

Abbreviations

AAL automated anatomical labeling.

ADHD attention deficit hyperactivity disorder.

ASSR auditory steady-state response.

BEM boundary-element model.

EEG electroencephalography.

EOG electrooculogram.

ERF event-related field.

ERP event-related potential.

fMRI functional magnetic resonance imaging.

HPI head position indicator.

IFG inferior frontal gyrus.

IQ intelligence quotient.

ISC inter-subject correlation.

LDN late discriminative negativity.

MEG magnetoencephalography.

MMF mismatch field.

MMN mismatch negativity.

MMR mismatch response.

MNE minimum-norm estimation.

MNI Montreal Neurological Institute and Hospital.

MRI magnetic resonance imaging.

RM-ANOVA repeated-measures analysis of variance.

ROI region of interest.

STG superior temporal gyrus.

VBM voxel-based morphometry.

WAIS-IV Wechsler Adult Intelligence Scale (fourth edition).

WMS-III Wechsler Memory Scale (third edition).

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1 Introduction

> Reading is important, because if you can read, you can learn anything about everything and everything about anything.
>
> *Tomie dePaola*

In human culture, reading and writing emerged around 5000 years ago, which make them evolutionarily modern skills [1]. Reading and writing employ complex neural networks, making them arguably some of the most sophisticated skills that the human brain has developed. Nowadays, literacy, the ability to read and write, is a basic human right [UNESCO, 2]. This highlights the importance of providing adequate support for individuals with difficulties in reading and writing, such as in the most common learning disorder developmental dyslexia. The achievement of this goal is supported by investigating the neural basis of the difficulties. This thesis aims to determine how brain function and structure differ in those with dyslexia compared to typical readers, and how these differences relate to reading skills.

1.1 Developmental dyslexia

Developmental dyslexia (henceforth dyslexia) is a heritable learning disorder affecting the reading and writing skills of about 4–17 % of the population [3, 4], impacting individual academic achievement and emotional well-being, as well as posing an economic burden in health care and education [5]. Dyslexia is specifically defined as an impairment in word recognition and spelling, despite adequate instruction and normal intelligence [6]. Being a disorder characterized by behavioural symptoms, dyslexia is at the low end of a continuum of reading ability with a non-specific cutoff point [7].

Dyslexic individuals typically have difficulties in decoding language, i.e., the mapping of native-language sounds to their orthographic counterparts (letters), but not in speech comprehension [8].

Dyslexia has a moderate heritability of ≈50 % [for a review, see 9]. Several candidate genes have been identified to date whose variant function can cause subtle malformations in the cortex that could be related to the migration of immature neurons as well as their connections [for a review, see 10]. The exact pathways from dyslexia gene variants to neural deficits are largely unknown. However, recent evidence suggests that cortical network abnormalities caused by gene variants could lead to neural deficits in speech processing in speech-trained animals, as is characteristic of dyslexia [11, in rats]. These are promising steps towards understanding the complex genetic background of dyslexia.

Not only the pure genetic background, but also an active relationship between genes and environment adds to the risk factors to develop dyslexia. The environmental predictors of dyslexia include, but are not limited to, socioeconomic status, home literacy environment, consistency of the learned language, and early language exposure [8, 12]. Understanding both genetic and environmental risk factors will enhance the identification of individuals at highest risk and the development of targeted preventive and interventive measures.

Dyslexia can occur together with other disorders. This comorbidity includes attention-related disorders, such as attention deficit hyperactivity disorder (ADHD) and attention deficit disorder, (specific) language impairment or developmental language disorder, speech sound disorder, and other learning disorders impacting reading comprehension, math (dyscalculia) and writing [13, 14, for a review, see 8].

The neuropsychological profile related to the reading deficit in dyslexia has been studied extensively, and it is known that both reading and several reading-related cognitive functions are affected (Section 1.1.1). There have been several attempts to explain the complex underlying deficits in dyslexia, some of them connected to neural-level evidence. Two such theories that have received significant interest are the phonological deficit theory and the temporal sampling deficit theory (Section 1.1.2).

1.1.1 Reading-relevant skills and their impairments in dyslexia

Reading is universally defined by mapping written symbols (letters in alphabetic languages) to their corresponding speech sounds [15]. Therefore, it requires a successful integration of sensory inputs and acquired processing as well as analysis skills to decode and understand print. Skills and knowledge relevant for learning to read can coarsely be divided into 'core processes' that directly involve linguistic processes, and other more remotely related factors (Figure 1).

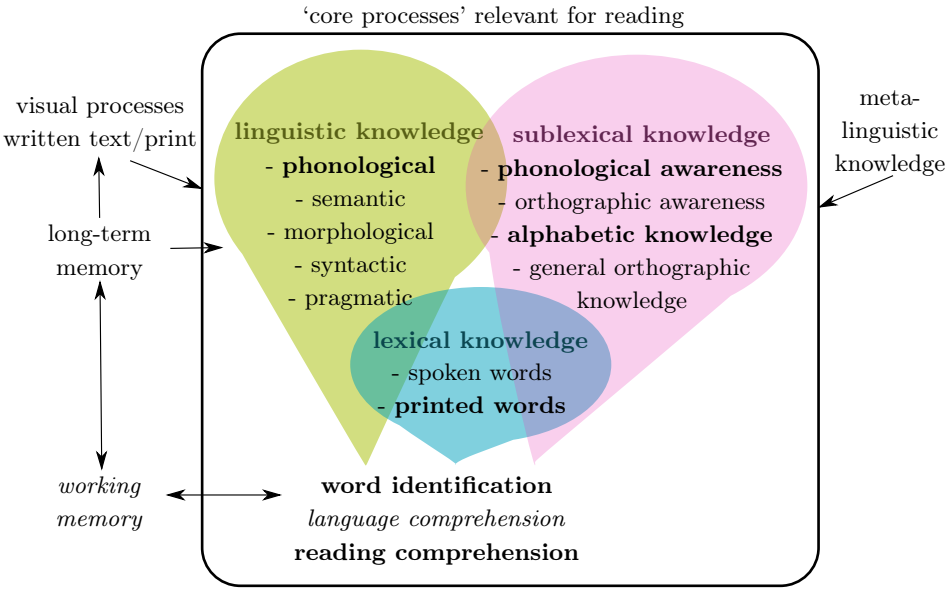

Figure 1: *Cognitive processes and knowledge required for reading acquisition.* ***Bold*** *marks refer to the most often found deficiencies in dyslexia, and italic marks to less often found deficiencies. Adapted with permission from [16].*

Normal reading requires fluent word identification and language comprehension [17, Figure 1, bottom inside the box]. These skills are built by the three 'core processes' relevant for reading: *linguistic, sublexical, and lexical* knowledge and coding [16, Figure 1, three coloured areas inside the box].

First, *linguistic* knowledge enables successful language acquisition and use (Figure 1, left green area). Linguistic coding can be subdivided into the fol-

lowing processes: phonological processing, i.e., use of speech sounds; semantic and morphological processing, for extracting meaning; syntactic processing, i.e., how words combine into phrases and sentences; and pragmatic processing, i.e., the means to use language. Secondly, *sublexical* (letter-level) knowledge (Figure 1, right lilac area) consists of phonological awareness, i.e., rules in spoken language, such as the knowledge that speech sounds and its combinations (syllables) make up words; orthographic awareness, i.e., rules in written language; alphabetic knowledge, i.e., letters; and general orthographic knowledge, i.e., rules of the alphabetic writing system. Thirdly, *lexical* (word-level) knowledge requires understanding of spoken and printed words (Figure 1, bottom blue area). Knowledge and coding related to these three 'core processes' as well as their successful integration are critical for effortless and fluent reading. Within the core processes, the best predictors of reading ability from onset of literacy instruction to around ten months of instruction are letter knowledge (alphabetic knowledge), phoneme awareness (part of phonological awareness focused on the smallest units of speech sounds), and rapid naming skills [orthographic knowledge and/or phonological processing; 18, for reviews, see 19–21].

Other relevant processes for reading influence these 'core processes' directly or indirectly (Figure 1, outside the box). For example, visual processes are required to identify written letters and words (print). Long-term memory is required for various processes, such as retrieval of grammatical rules, word meanings, and previous subject-specific knowledge required to extract meaning. Working memory temporarily encodes, stores, and retrieves information to manipulate and integrate it from several sources [22]. The phonological loop of working memory is further thought to form links between units of spoken and printed words which aids phonological processing [16, 23]. Metalinguistic analysis is another skill relevant for reading and is described as the analysis of language structures, i.e., grammar.

The basic deficit in dyslexia lies in letter-to-sound decoding, i.e., correspondences of individual letters and sounds, as well as slower and less accurate word identification and spelling (alphabetic knowledge), leading to worse reading comprehension [for reviews, see 8, 16, 24]. The concepts describing these most common deficiencies in dyslexia are marked in **bold** in Figure 1. Less common deficiencies include difficulties in language comprehension [25]

and working memory, particularly verbal working memory [19, 26]. Working memory is currently seen as a factor that might influence dyslexia by its moderating effect, but is not likely to be causal [27]. Furthermore, it has been suggested as a risk factor which can enhance dyslexia, especially in combination with phonological processing deficits [26]. These less common impairments are marked in *italics* in Figure 1. Not included in the Figure, but nevertheless noteworthy, are attentional processes that have been proposed to play a role in learning to read and in dyslexia [24]. A combination of these more or less common impairments leads to slower and less accurate reading [21, 28].

1.1.2 Neural theories of dyslexia

Several theories aim to explain the origins of dyslexia, starting at the genetic and cellular level, via the neural theories, and ending in possible sensory and cognitive explanations [for reviews, see 29–32]. The aim of this section is to explain the two neural-cognitive theories that are most relevant for the neural evidence investigated in this thesis: The phonological processing deficit theory and the temporal sampling deficit theory. No single theory can likely explain all possible facets of dyslexia, as it includes a multitude of phenotypes that can be influenced by a range of genetic and other factors [33, multiple deficit theory, 34].

The first theory is based on phonological processing (Section 1.1.1). Successful phonological processing is the basis for learning to read and write [16]. In dyslexia, phonological processing is weakened, including both phonological awareness and phoneme awareness [19]. This *phonological deficit* [4, 35–37] is potentially caused by abnormalities in structure and function in the left hemisphere of the brain [38]. These abnormalities could directly weaken the neural representations of speech sounds [36], or their accessibility [30, 39, 40]. Numerous studies have given support to this theory by investigating neural speech-sound processing and its possible atypicalities in dyslexia (see 1.2.1.1). Two studies in this thesis investigated whether dyslexic or at-risk groups exhibit atypical neural speech-sound processing, thought to reflect phonological processing problems. Critics note the circular nature of this theory, i.e., that phonological problems are the defining

symptom and the underlying cause of dyslexia [41].

The second theory is based on the temporal aspect of speech encoding. Speech perception and processing have been proposed to be based on temporal coding via neuronal oscillatory networks at different frequency ranges [42, 43]. If the neural temporal coding of some aspects of the speech signal is 'out of rhythm', it can lead to inaccurate parsing of speech, which in turn can lead to impaired phonological representations [44]. The *temporal sampling deficit* has been suggested to lie primarily in low-frequency oscillatory networks, i.e., theta and possibly delta ranges [45]. Frequencies in the theta range (4–10 Hz) primarily synchronize with the rhythmic occurrence of syllables in speech and the delta-frequency band (1.5–4 Hz) is thought to parse prosody via stressed syllables in speech [43]. An inaccurate temporal sampling of speech in low-frequency oscillatory networks is consequently thought to explain difficulties in dyslexia with syllable parsing, syllable stress, and phonetic aspects of syllables. This theory has gained support by findings of impaired rise time discrimination [46, 47], impaired syllable stress perception [47, 48], as well as impaired rhythm perception at the rate of syllables in speech in dyslexia [49, 50]. In addition, several studies investigating neural oscillations have found abnormalities in dyslexia (see 1.2.2.1). One study in this thesis investigated a specific aspect of neural oscillatory activity during speech processing and its possible atypicalities in dyslexia that could reflect problems in temporal sampling of speech. Critics note that not all studies give consistent support to this theory [51], and a possible causal link between temporal sampling deficits and impaired phonological representations remains to be established [30, cf. 44].

1.2 Neural speech and speech-sound processing in dyslexia

According to the neural theories (Section 1.1.2), dyslexia is characterized by a neural speech-processing deficit. Neural speech and speech-sound processing can be probed non-invasively with neurophysiological measurements of electric currents and magnetic fields in the brain, with electroencephalography (EEG) and magnetoencephalography (MEG), respectively. Both

are direct measures of brain activity, specifically the postsynaptic currents of synchronously firing cortical neurons [52]. Brain activity can, e.g., be recorded to repeating stimuli (event-related paradigms, see Section 1.2.1), or continuously during task or rest (Section 1.2.2). The nature of these two approaches, as well as previous findings in dyslexia on neural speech and speech-sound processing together with their associations to reading and related measures are reviewed in the following sections.

1.2.1 Neural speech-sound discrimination

Neural speech-sound processing can be investigated with EEG and MEG (see Section 1.2) using event-related paradigms. A typical auditory event-related paradigm consists of sounds that repeat many times, and the neural responses averaged across these trials around the onset of the sound (stimulus onset) are referred to as event-related potential (ERP) and event-related field (ERF), in EEG and MEG, respectively. Even though other ERP and ERF components have been studied in dyslexia [for a review, see, e.g., 53], a majority of studies in this field has focused on the mismatch negativity (MMN), and magnetic MMN, followingly referred to as mismatch field (MMF), which are types of auditory event-related responses that will be focused on also in this thesis.

MMN is an automatic neural change detection response that is elicited when a repetitive aspect in the stimulus stream is violated [first reported by 54]. MMN can be elicited by simple acoustic changes in tones [for a review, see 55], but also by more complex changes in tones and relationships between them [for a review, see 56]. Furthermore, MMN is elicited by changes in speech sounds [for a review, see 57]. Importantly, it reflects long-term representations of phonemes in the native language [58]. Therefore, MMN has been frequently used to investigate non-speech and speech discrimination in dyslexia (Section 1.2.1.1).

Even though attention processes can influence its properties [e.g., 59], MMN can be obtained without attention to the stimuli [60], e.g., during sleep [61], making it a valuable tool for studies on children and infants (Section 1.2.1.2). It is best described in the auditory domain [for a review, see 55], but has also

been measured in other domains [e.g., visual MMN, 62, 63]. A typical auditory paradigm involves frequently repeating 'standard' stimuli and rarely occurring 'deviant' stimuli that differ in their acoustical properties from the standard. If the deviance is detected by the brain, MMN is elicited.

Different underlying mechanisms of MMN generation have been proposed. The model adjustment hypothesis posits that the incoming auditory stimulus is compared to previous memory traces, and a violation of this expectation results in the elicitation of the MMN, leading to an update of the expectation [64–67]. Alternatively, it has been suggested that MMN reflects an excitement of a previously adapted, i.e., less sensitive and less firing, neuronal population by a (novel) deviating stimulus [68, 69]. However, it has been ruled out that adaptation alone could be the underlying mechanism of MMN generation [70]. The predictive coding framework unifies these two theories by regarding the brain as a hierarchical system in which information is integrated between each level in both directions, bottom-up and top-down [71]. Within this framework, the MMN would result from a prediction error of the sensory input, as the unexpected deviant stimulus is processed, leading to an updated prediction of the (auditory) world. The circle of updating predictions based on the sensory input (bottom-up), and sending updated predictions (top-down) leads to optimized predictions [72].

MMN can be seen in the deviant-minus-standard ERP, typically as a negative deflection at 100–250 ms after the onset of the change and is distributed fronto-centrally over the scalp when referenced to mastoids or nose [55]. The accuracy of change discrimination is reflected in the MMN amplitude and latency [73–75; for a review, see 76]; the more accurate or faster the discrimination, the stronger the amplitude and the shorter the latency.

A temporal-frontal network governs the MMN, with main generators located in the bilateral temporal cortices [77–80] and the prefrontal cortex [58, 77, 78]. They are associated with sensory processes and cognitive comparative mechanisms, respectively. The prefrontal cortex generators were suggested to indicate an attention shift upon change detection [77, 81].

A response equivalent to the adult MMN, referred to as mismatch response (MMR), can be measured already in newborn infants [82], and even before birth [83]. The immaturity, plasticity, and rapid development of the infant

brain affect the MMR and therefore it can differ from the adult MMN in polarity: the 'negativity' can be a 'positivity' in infant MMRs [84]. It is thought that positive MMRs indicate immaturity of the auditory change detection system [85, cf. 86], and that during development positive polarities slowly converge into adult-like negative polarities [87–91]. Positive MMRs have alternatively been suggested to reflect novelty detection and to mature into adult P3a responses that index auditory attention [92]. Positive and negative MMRs can co-occur [93] and may reflect distinct neural processes [88, 91] that are nevertheless attributed to genuine change discrimination [91, 93, 94], even though the exact generation of the responses remains unclear. MMRs have been reported to non-speech stimuli, such as frequency and duration changes in tones [82, 93, 95, 96] and more complex rule changes in tone patterns or musical chords [97, 98], as well as to speech sounds, such as vowel, consonant, and duration changes in syllables and pseudowords [99–103]. These results show that the infant brain is prepared for the auditory and linguistic world, making this method promising to also tap into possible early auditory/speech discrimination deficiencies in infants at risk of dyslexia (Section 1.2.1.2).

1.2.1.1 MMN/MMF in dyslexia

Dyslexia is characterized by a neural auditory/speech discrimination deficit, shown by diminished MMN/MMF amplitudes and delayed latencies in adults and children [for reviews, see 104–106], and even infants at heightened risk [107, see Section 1.2.1.2]. MMN/MMF studies on dyslexia using non-speech and speech stimuli with adult participants are summarized in Table 1.

Results on the discrimination of non-speech stimuli are mixed. To tone frequency changes, deficient neural discrimination has been reported in dyslexic adults, evidenced by diminished MMN/MMF amplitudes and delayed latencies [108–111, however, see 112]. Also in dyslexic or at-risk children, most results speak for a tone frequency discrimination deficit [113–117, however, see 118–120]. Mixed results have been obtained regarding tone duration discrimination with missing or diminished MMN [109, 121, respectively], intact MMN [108, 122], or even enhanced MMN [113] in dyslexic or at-risk children and dyslexic adults. A study with several 'simple' feature

Table 1: *Overview of mismatch negativity (MMN)/mismatch field (MMF) studies in adults with dyslexia.*

Ref	N_{DYS}/N_{CON}	*Stimuli*	*Results*
[108]	10/10	frequency and duration changes in pure tones	reduced and delayed MMN to small, but not large frequency changes in DYS, but not to duration changes
[125]	15/20	duration pattern changes in pure tone sequence	reduced late MMN in DYS
[126]	8/8	duration pattern changes in silent intervals; duration change in silent intervals	missing/reduced MMN in DYS to duration pattern changes; bilateral late MMN in DYS, right-dominant in CON to duration pattern changes
[112]	12/13	frequency changes in pure tones and consonant changes in syllables	absent and reduced late MMN in DYS to consonant changes, but not to tone-frequency changes
[111]	8/11	frequency changes in tones	reduced left MMF in DYS, right-lateralized MMF in DYS
[110]	8/8	frequency changes in pure tones and tone pairs, tone pattern changes in tone pairs	reduced left MMN in DYS to frequency changes in pure tones, but not in tone pairs; absent and reduced MMNs in DYS to tone following, but not preceding the tone pair
[109]	9/11	frequency, duration, intensity, location, and gap changes in harmonical tones	absent MMN in DYS to frequency and duration changes; reduced MMN in DYS to frequency changes, enhanced MMN in DYS to location changes; no abnormal MMN in DYS to intensity and gap changes
[123]	6/6	tone omission in sequence of pure tones	reduced MMF in DYS
[124]	10/9	frequency-modulation changes	reduced MMN and late MMN for 20 Hz modulations in DYS, but not for 5 and 240 Hz modulations

Notes: Studies with healthy adults (older than 18 years) measuring MMN/MMF to non-speech and speech stimuli and having a group with dyslexia (or a broader definition that includes dyslexia) and a control group are included. Studies only reporting event-related potentials to standard and deviants were excluded. Ref – Reference, DYS – dyslexic group, CON – control group.

changes in harmonical tones within one paradigm reported that MMN was enhanced to location changes, normal-like to intensity and gap changes, and diminished to frequency changes in dyslexic adults [109]. Reduced MMNs/MMFs have also been found to tone omissions [123] and frequency modulations [124].

In addition to several discrimination deficiencies of 'simple' tone features, also more complex paradigms have shown abnormal processing in dyslexia. For example, missing or diminished MMNs were found to duration pattern changes [125, 126] and tone pattern changes [110], suggesting that the sound environment might have interfering or masking effects on neural auditory processing in dyslexic adults. Taken together, dyslexia seems to be characterized by basic auditory discrimination deficiencies, although also controversial findings have been repeatedly reported. This is in line with the suggestion that only ≈40 % of individuals with dyslexia have basic auditory processing deficits [106].

The neural discrimination of speech stimuli in dyslexia as compared to the aforementioned non-speech ones has been investigated more rarely. In adults, the only study using speech sounds so far has found diminished MMN to a consonant change from /*da*/ to /*ga*/ [112]. In studies on dyslexic or at-risk children, relatively heterogenous results have been reported around the age of reading acquisition [for a review, see 127]. They had diminished MMN amplitudes to consonant changes in syllables, such as /*ba*/ vs. /*da*/ [115, 128, however, see 129], and /*te*/ vs. /*pe*/ [121]. Prereaders at risk of dyslexia had reduced MMN amplitudes to vowel identity /*te*/ vs. /*ti*/ and vowel duration changes [121], whereas another study reported comparable response amplitudes to phoneme changes /*o*/ vs. /*e*/ in dyslexic and control children [113]. These relatively mixed results suggest that some aspects of speech discrimination could be impaired in at least some individuals with dyslexia or at risk. Others may have intact speech discrimination, or other speech processing impairments that MMN may not be susceptible to.

MMFs have been far less used than MMNs to investigate auditory/speech discrimination in dyslexia. To date, results of only two studies have been reported. One found weaker MMFs to tone frequency changes in the left

hemisphere of adult dyslexic readers than controls [111], and another one found no MMF amplitude or latency differences between dyslexic children and controls to syllable changes /*ba*/ vs. /*da*/ [129].

It is unclear whether dyslexia is accompanied by an atypical hemispheric lateralization of MMN or MMF, as the findings appear to be highly inconsistent. The left hemisphere has been suggested to be dominant during language processing in typical readers [130], and left-hemisphere cortical abnormalities have been related to dyslexia [131, 132]. Some evidence indicates altered lateralization of the MMN to non-speech-sound changes in dyslexia [110, 111, 122, 126, 133–136, however, see 109, 112, 117, 125]. Speech-elicited MMN lateralization has been investigated less. Such MMNs were not differently lateralized between dyslexic and control groups in adults [112, 120, 135]. However, in prereaders, lateralization differences were found, the MMN to phoneme changes being left-lateralized in controls and slightly right-lateralized in at-risk children [116].

1.2.1.2 MMR and dyslexia risk

While MMN/MMF findings from adult studies may reflect other than genetic influences, e.g., environmental ones, research in early infancy can investigate the genetic influence best, due to still minimal environmental influences, such as language exposure. A higher genetic risk to develop dyslexia has been related to certain gene variants and their combinations [10]. Table 2 gives an overview of infant MMR studies that compare infants (here defined as age of 0–12 months) at risk of dyslexia with low-risk controls. The risk status is usually defined by a familial background of dyslexia. This familial background can be checked from a dyslexic family member, usually by self-report or dyslexia diagnosis of a parent and/or other close relatives, a history of reading difficulties in childhood, and below-norm performance in reading-skill tests, such as word, pseudoword, text reading, and spelling [e.g., 137–139]. The exact definition can vary between studies.

Table 2 demonstrates that MMR dyslexia risk studies are scarce, showing a consistent pattern of smaller or absent MMRs in the at-risk compared to control groups to duration and consonant changes in speech sounds and

Table 2: *Overview of mismatch response (MMR) studies in infants at risk of dyslexia.*

Ref	*Age*	N_{DYS}/N_{CON}	*Stimuli*	*Component*	*Result*	*Alertness*
[137]	6	25/27	duration changes in syllables	late negative MMR	smaller MMR in left hemisphere in DYS	awake
		12/12	duration changes in syllables	late negative MMR	absent MMR in DYS	
[138]	2	32/18	consonant changes in syllables	early positive MMR and late negative MMR	absent MMRs in DYS	quiet sleep
[140]	6	13/30	frequency changes in complex tones	early positive MMR	smaller MMR in fronto-central and left channels in DYS for short, but not long inter-stimulus intervals; no group differences in latency	awake
[139]	2	82/57	consonant changes in syllables	early positive MMR and late negative MMR	diminished early and absent late MMR in DYS	quiet sleep

Notes: Studies with healthy full-term infants (up to 12 months of age) that measure MMR to non-speech and speech stimuli and having a group at risk of dyslexia (or a broader definition that includes dyslexia) and a control group are included. Age is presented in mean months. Studies only reporting event-related potentials to standard and deviants, or infant studies that linked early brain measures with later reading skills were excluded. Ref – Reference, DYS – dyslexia-risk group, CON – control group.

frequency changes in complex tones [137–140], some studies reporting this effect to be specific to the left hemisphere [137, 140]. In addition to this abnormal speech discrimination, infant ERPs to deviant stimuli have been described to be atypical in at-risk infants [100, 141]. Recent meta-analyses suggest that auditory ERPs/MMRs are sensitive to distinguish at-risk from control groups in infancy with medium to large effect sizes [127, 142].

The lateral distribution of the MMR has been found to differ in infants at familial risk of dyslexia [139, 141, 143, 144, some studies only reporting ERPs to standards and deviants], with, e.g., diminished MMR in the left hemisphere of the at-risk group [139]. However, similarly as in MMN studies with dyslexic adults, findings are inconsistent. This may be attributed to differences in risk definition, sleep stage during the recording [145], and sample size. A sufficient sample size is even more important in infant than in adult studies, because first, only a part of the infants at risk of dyslexia will also develop it later [146, 147], and second, infant ERPs are extremely variable within and between subjects [86, 148].

1.2.1.3 Associations of MMN and MMR with reading-relevant skills

Evidence of MMN/MMR as a neural marker for dyslexia is supported by findings that its response amplitudes are also associated with language and reading skills in adults and children [73, 108, 117, 149–151]. Several studies suggest that MMN reflects phoneme and phonological skills in typically-reading and reading-impaired children. For example, MMN amplitudes to changes in speech sounds have been positively associated with phoneme and phonological processing skills in typically developing prereaders [150] and in children with, without, and with compensated reading disorder [117]. MMN can even serve as a marker of reading development, as suggested by two intervention studies in children with reading difficulties, in which improvement of reading or related skills correlated with increases in MMN amplitudes [73, 149]. Even though investigated more rarely, also in adults links between MMN and reading skills were found: Across dyslexic and typical readers, more reading errors were associated with longer MMN latencies to tone-frequency changes [108], directly linking reading/phonological per-

formance with neural processing speed.

Moreover, working memory skills correlated with the late discriminative negativity (LDN) amplitude, which is a change-related ERP component with a longer latency than MMN, mostly in children [152], to tone frequency deviants in preschool children at risk of dyslexia and controls [153]. Another study reported a correlation between better working memory performance and increased frontal MMN to intensity deviants in adults [151]. These studies reveal the potential of MMN to reflect working memory skills in general, and their impairments in dyslexia.

Next to the associations of MMN with reading skills measured at the same age, speech-elicited MMRs or MMNs in infants and children are promising predictors of later language skills [for reviews, see 127, 142]. Absent and diminished MMN/MMRs [154–158], even in infancy [155–157] relatively consistently predict worse reading and language outcomes. For example, absent MMRs to consonant changes in two-month-old infants at familial risk of dyslexia predicted worse reading fluency in school [156], showing the potential of infant MMRs to predict dyslexia. Similarly, absent negative MMRs to consonant changes in syllables at five months of age were associated with later writing problems [157]. Forecasting language and reading development and their possible delays or difficulties in the future from early neural responses may help in targeting early support. Early auditory ERPs (including, but not exclusively MMRs) provide the opportunity to obtain these neural responses in nonverbal children and infants, long before any early language skills could be behaviourally measured.

1.2.2 Neural processing of natural speech

Brain research on dyslexia has largely used paradigms with a controlled way to present stimuli, typically including repetitive sounds (Section 1.2.1). Due to this, the paradigms are often unnatural to listen to. The ecological validity of findings of neural speech processing can be increased by using more natural, real-life stimuli, such as continuous speech.

Natural stimuli have been introduced to human neuroscience around 20

years ago [159–161] and have since proven viable to investigate several aspects of speech processing [162–167, for reviews, see 168, 169]. Inter-subject correlation (ISC) is a relatively recent method that has proven feasible when utilizing natural stimuli [170]. It is a model-free, stimulus-driven analysis approach that extracts the shared neural activity across participants [171]. The shared cortical activity reflects the time-varying dynamics of the natural stimulus that in speech can consist of various acoustic, phonological, syntactic, and semantic features that change over time [172]. Shared neural activity in social context has been suggested to reflect similar understanding and goal-directed behaviour [173].

ISC has been applied successfully with various natural stimuli, e.g., movies [170, 174–176], speech [162, 172, 177–179], and music [180–182], mostly in functional magnetic resonance imaging (fMRI). ISC studies with natural speech stimuli and fMRI have found that not only low-level auditory regions synchronize between listeners (such as bilateral temporal areas), but also higher-order regions (such as frontal, parietal, and midline areas), suggesting comparable higher-level processing and perception of speech across different people [162, 172, 177–179]. This apparent hierarchy in brain processes was suggested to correspond to time scales in the speech signal, short-scale immediate input being processed in low-level auditory areas, and longer time scales, such as sentences and paragraphs, in higher-order regions [177]. It was further demonstrated that synchronized brain activity between speakers and listeners increases understanding (quantitative measure of story comprehension) and the success of communication [162], and that the production and comprehension processes during communication are neurally coupled [178]. A recent article shows that ISC is also connected to behavioural (working memory) and personality measures [183]. This link of ISC to behaviour makes it promising to investigate the relation between ISC and reading-relevant skills in dyslexia.

Compared to its abundance in fMRI studies, ISC has only rarely been applied in MEG, the studies being limited to movie [175, 176, 184] and music stimuli [182]. Applied to MEG instead of fMRI, ISC could shed light on the more fine-grained temporal dynamics of speech processing, as the MEG signal can be divided into different frequency bands. Although promising, ISC has not yet been applied to investigate natural speech processing with MEG

in dyslexia. Therefore, findings obtained with MEG using other methods are valuable to look into different MEG frequency bands and their relevance for natural speech processing. One common method is used to analyze neural entrainment of cortical oscillations to speech [e.g., 42, 163, 164, 185, 186, for reviews, see 43, 167, 187]. Cortical oscillations are periodic waves of neuronal activity due to synchronous firing of a large number of neurons and can be understood as internal rhythms in the brain. They can occur at different rates, i.e., frequencies, and were suggested to be related to many higher-order brain processes [for reviews, see 188, 189]. Neural entrainment, on the other hand, can be defined as the synchronization of cortical oscillations to external rhythms in the (speech) stimulus.

Cortical oscillations in different frequency bands were proposed to have distinct roles when parsing the speech signal [e.g., 45, 168, 190, 191, for a review, see 43, summarized in Table 3, left]. They are not only parsing low-level auditory speech features, but are also meaningful for understanding speech. For example, theta phase patterns were found to be more reliable, the better a sentence was understood [42]. Even though oscillatory activity in different frequency bands has been mapped to certain functions during speech processing, it should be noted that cortical oscillations are by no means domain-specific [43]. They rather entail complex, high-dimensional dynamics in the brain that have been suggested to have various functions, however, in their entirety they are still poorly understood [for a review, see 192].

1.2.2.1 Neural characteristics of natural speech processing in relation to dyslexia and reading-relevant skills

Neural entrainment has been found to be abnormal during speech processing in dyslexia in several frequency bands [for a recent review, see 193, summarized in Table 3, middle]. The perhaps most consistent (as replicated, see Table 3) results are sampling deficits and atypical lateralization in delta and theta bands (low-frequency bands), as well as atypical lateralization in the low-gamma band, supporting the proposed temporal sampling deficits in dyslexia [45, see Section 1.1.2]. Furthermore, faster than normal sampling rates in high-gamma frequencies have been reported [194].

Table 3: *Frequency bands of neural oscillations and entrainment to speech stimuli, their abnormalities in dyslexia, and association with reading-relevant skills.*

Freq. band	*Role in speech processing*	*Abnormality in dyslexia*	*Association*
delta (0.5–4 Hz)	encoding of prosody (intonational phrase boundaries) and syllables [168, 197, 199]	sampling deficit [45, 50, 197, 200, 201] atypical lateralization [198, 202]	∼ worse PA [200, 201]; ∼ worse WM [201]
theta (4–8 Hz)	parses edges of the speech signal that correspond to syllable rate in speech [42, 168, 185, 203]	reduced sampling [45, 201] atypical lateralization [198, 204] stronger phase-locking [204] equally strong phase-locking, earlier phase [50]	∼ worse PA and worse WM [201] right-lateralized ∼ faster RS (CON) [204]
alpha (8–12 Hz)	upper range of syllabic rate [205]	reduced synchronization [196]	higher synchronization ∼ better PS (CON) [196]
beta (12–25 Hz)	phonemic rate [206]	enhanced synchronization [196] reduced synchronization [195]	∼ better PS (DYS) [196] ∼ worse PA [195]
low gamma (25–45 Hz)	phoneme-rate sampling, cross-frequency coupling with theta [168, 206, 207] syntactic/semantic processing [199]	atypical lateralization of entrainment [168, 194, 198, 204]	right-lateralized ∼ better PS and worse rapid naming skills (DYS) left-lateralized ∼ better PS and faster RS (CON) [194]
high gamma (55–90 Hz)	phonemic-categorical information sampling [208]	faster than normal rates in auditory cortices [194]	∼ worse WM [194]

Notes: If association was only found in one group, the group is indicated by CON – control group or DYS – dyslexic group. Freq. – Frequency, ∼ – associated with, PA – phonological awareness, PS – phonological skills, WM – working memory, RS – reading speed.

The reported abnormalities in dyslexia are relatively consistently in line with associations in the same studies with reading and related skills, mainly worse phonological skills or awareness, working memory and reading speed (Table 3, right). Even if these relations are not necessarily causal, they support the notion that temporal sampling deficits could lead to, or at least are related to worse phonological processing. However, also inconsistencies in both abnormalities in dyslexia and their correlations with reading-relevant skills have been found. For example, reduced [195] or enhanced [196] synchronization was reported in the beta band in dyslexia that was correlated with worse phonological awareness or better phonological skills, respectively. These and other inconsistencies can likely be attributed to differences in the use of stimuli, neuropsychological tests of reading-relevant skills, as well as substantial differences in the methods used to analyze speech-related oscillatory activity. Regarding the stimuli, only few studies used real speech [197, 198]. Together with the knowledge from neural entrainment studies, applying ISC offers good prospects to investigate natural speech processing and its possible abnormalities in dyslexia in different MEG frequency bands.

The neural speech and speech-sound processing atypicalities in dyslexia reviewed so far and their relation to reading-relevant skills (Section 1.2) are indicators of abnormal brain function. These functional abnormalities in the dyslexic brain are tightly coupled with and dependent on brain structures and their abnormalities related to dyslexia (Section 1.3).

1.3 Brain anatomy and dyslexia

Structural abnormalities in the brain of individuals with dyslexia were first observed in *post-mortem* studies [209, 210] and can nowadays be assessed *in vivo* and non-invasively with modern neuroimaging techniques, such as magnetic resonance imaging (MRI). According to a recent review, the most consistent anatomical finding is a reduced *total brain volume* in dyslexic individuals [meta-analysis 211]. While this is an important finding of a global neuroanatomical marker, it is rather unclear what it reflects – it is not related to lower intelligence quotient (IQ), and could be a risk factor of dyslexia, or a consequence of neurodevelopmental disruptions [211].

A commonly used automated technique to assess local brain structures is voxel-based morphometry (VBM) [212]. This method extracts voxel-wise grey- and white-matter concentrations in the brain. The following sections will mainly focus on VBM findings in relation to dyslexia, as they are especially relevant for this thesis.

The *volume of grey matter*, mainly consisting of neuronal cell bodies, their dendrites, neuronal supporter cells (glial cells), and synapses, has been reported to be reduced in several areas of the brain in dyslexia [213–219, however, also increase of grey-matter volume in 217]. Meta-analyses have identified consistent areas of reduced grey-matter volume in right superior temporal gyrus (STG), left temporal areas, and the cerebellum [132, 220, 221], while bilateral supramarginal gyri, left fusiform, and inferior temporal gyri were reported in only one meta-analysis [220], and left orbitofrontal cortex only in another one [221, see Figure 2].

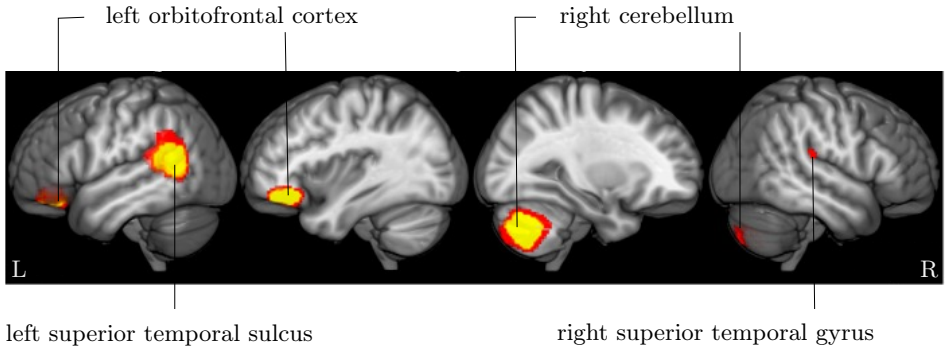

Figure 2: *Brain areas with grey-matter volume reductions in dyslexic readers from the most recent meta-analysis across eleven voxel-based studies of reading disability. Adapted from [221]. L – left hemisphere, R – right hemisphere.*

Previous meta-analyses of functional neuroimaging studies have linked most of these brain areas to reading functions or dysfunctions [132, 222, 223]. Convergence between structural abnormalities and underactivation in dyslexia during reading or related tasks have been reported for the left superior temporal sulcus that is responsible for phonological processing [meta-analysis 132]. Also a dyslexia risk gene variant has been associated with structural abnormalities in or close to the superior temporal sulcus that were in turn

associated with reading skills in typical and dyslexic readers [224, 225]. These studies propose a genetic influence for neuroanatomical development of the superior temporal sulcus. The relevance of right STG grey-matter reductions in dyslexia is less clear, but as such reductions are also apparent in at-risk children prior to reading onset, they may also be neuroanatomical abnormalities that are genetically driven, rather than results of reduced reading exposure [226, 227].

Volume of white matter, mainly consisting of myelinated axons, has been investigated less and therefore results are less replicated. Studies report reduced white-matter volume in dyslexic compared to control readers in left frontal and central areas [217, 228], a left temporo-parietal region [219], as well as right temporal areas [228, 229], and right frontal, central and subcortical regions [228]. Only one of these studies also reported higher white-matter volume in dyslexics than controls in the right hemisphere close to the putamen [228]. Abnormalities in left temporo-parietal regions in dyslexia were confirmed also in tractography studies that investigate white-matter microstructures [meta-analysis 230].

Additional neuroanatomical abnormalities in dyslexia have been found in other global brain measures, such as in total surface area of the brain [231] and cortical thickness [231–233]; however, these findings are less replicated than the total brain volume reduction [211]. Advanced multivariate pattern recognition tools have been used to classify dyslexic and typical readers from a combination of several neuroanatomical (and other) measures [234–238]. This shows that anatomical brain abnormalities in dyslexia are likely not constrained to a single brain structure, but rather entail a combination of aforementioned several local and global brain structures that can be obtained from MRIs.

1.3.1 Associations of brain structures with reading-relevant skills

Most of the anatomical structures that have been shown to be atypical in dyslexia (Section 1.3) are also associated with the reading network of the brain. Faster and/or more accurate *word and pseudoword reading* corre-

lates with several different neuroanatomical measures [214, 215, 217, 218, 235, 239–242, for a review, see 221]. Most consistent correlations were found between better word-reading skills and higher grey-matter volume in left superior temporal regions and the left orbitofrontal cortex across twelve studies, regions also identified to have reduced grey matter in dyslexia in the same meta-analysis [221, Figure 2]. In another study, abnormally increased grey matter in the left inferior temporal gyrus was found in dyslexia and correlated with slower reading speed [217]. However, correlations between word reading and grey-matter volume were absent in a large sample of typical readers in areas associated with grey-matter atypicalities in dyslexia [243], suggesting that these areas might not have the same relevance for reading in typical compared to dyslexic readers. A combination of better word reading, spelling, and comprehension was found to be predicted by higher grey-matter volumes in left frontal and temporal, as well as right occipito-temporal regions that are part of the reading network [244]. Better reading skills were further associated with higher white-matter microstructural integrity in left temporo-parietal and left frontal regions [meta-analysis 230, in line with abnormalities in dyslexia].

Phonological processing skills [such as phoneme deletion, 235, phonological decoding and naming speed, 242] show both positive and negative correlations with grey-matter volume. For example, better skills were associated with more grey matter in the STG and inferior frontal gyrus (IFG) [235], left parietal lobe, right occipital, and right frontal parts of the brain [242]. However, better reading skills were also associated with less grey matter in the cerebellum [235] and left precuneus [242]. Faster rapid naming skills [245] and better phoneme awareness [246] were associated with better integrity of white-matter microstructures in left temporo-parietal regions, while both positive and negative correlations in these regions were reported for phonological awareness [247, 248]. Correlations of phonological processing skills with anatomical neural measures seem to therefore vary between the different phonological tests.

Verbal *working memory* was suggested to positively correlate with white-matter volume in fronto-parietal regions [249]. Tractography studies additionally suggested positive associations between working memory and white-matter microstructure in bilateral frontal tracts [250], the parietal cortex,

and corpus callosum [251].

To conclude, several neuroanatomical structures have been related to reading, phonological processing, and working memory performance. Most often, better reading-relevant skills correlated with larger or more integrated brain structures in left temporal, left temporo-parietal, as well as bilateral frontal areas.

2 Objectives

This dissertation aimed to investigate functional neural correlates of dyslexia or its risk by inspecting neural speech processing in adults and newborn infants. Moreover, it aimed to examine the neuroanatomical correlates of dyslexia, and the associations of functional and anatomical neural correlates with reading and related skills.

Specifically, I investigated

- neural speech-sound discrimination of frequency, duration, and vowel changes in pseudowords in dyslexia risk and dyslexia with MMRs and MMFs (Studies I and II),
- neural ISC during natural speech processing in different frequency bands and its atypicalities in dyslexia (Study III),
- grey- and white-matter volume correlates of dyslexia (Study IV), and
- associations of reading, phonological processing, and working memory skills with neural speech and speech-sound processing (functional, Studies II and III) and anatomical findings (Study IV).

Based on previous findings, the hypotheses were:

- Newborns at familial risk of dyslexia have absent or diminished MMRs to speech-sound changes (Study I), reflecting weak neural speech discrimination (phonological deficit theory).
- Adults with dyslexia have weaker MMFs to speech-sound changes (Study II), reflecting weak neural speech discrimination (phonological deficit theory).
- Adults with dyslexia have reduced ISCs in low frequency bands and enhanced ISCs in high frequency bands (Study III), reflecting atypical

neural synchronization suggesting temporal sampling deficits (temporal sampling deficit theory).

- Adults with dyslexia have a reduced total brain volume, reduced grey matter in left and right temporal areas, as well as the cerebellum, and reduced white matter in left temporo-parietal, bilateral frontal and central, as well as right temporal and subcortical midline regions (Study IV), reflecting weaker neuroanatomical structures relevant for reading.

- Reading, phonological processing, and working memory are correlated with MMFs, ISCs, and anatomical measures (Studies II–IV), the direction of the correlations expected to be in line with findings of group differences.

3 Methods

The studies of this thesis were parts of two larger projects: Study I was part of the longitudinal project *The neural basis, biomarkers, and amelioration by intervention of language and reading disorders* which aims to investigate children's language development and the influence that dyslexia risk has on it. Studies II–IV belonged to the adult dyslexia project *Speech and short-term memory functions in dyslexia* which has been preregistered at clinicaltrials.gov (identifier NCT02622360).

3.1 Participants

Newborn infants with or without an elevated risk of dyslexia participated in Study I (Table 4). An infant was considered to have an elevated risk of dyslexia, when at least one biological parent had moderate to severe dyslexia. This was confirmed by below-norm performance (at least two standard deviations, SD) in reading or writing speed or accuracy in at least two subtests [252, Section 3.3.1]. In addition, evident reading problems in childhood had to be identified in an interview and some parents had a recent diagnostic statement of dyslexia from a health-care professional. Control infants were selected from families without any evident language-related impairments and the groups were matched for gender and age at measurement.

Healthy Finnish adults aged between 18 and 44 years and without neurological diseases participated in Studies II–IV (same sample, see Table 4). About half had a diagnosis of dyslexia from a health-care professional or were considered dyslexic, because they performed below norm (at least 1 SD) in reading speed or accuracy in at least two subtests [252, Section 3.3.1], and the other half had no history of language-related disorders. Exclusion criteria were attention deficits tested with the Adult ADHD Self-Report Scale [253], neurological or psychiatric disorders, a special school curriculum, both

assessed with background questionnaires, and a performance IQ below 80 tested by Wechsler Adult Intelligence Scale (fourth edition) (WAIS-IV) [254, see 3.3.1].

Table 4: *Background information for participants of all Studies.*

Study	*Total N*	N_{DYS}/N_{CON}	*Gender (f/m)*	*Age*
I	88	44/44	38/50	9.0 ± 4.5 days
II	43	21/22	24/19	30.4 ± 7.3 years
III	44	23/21	23/21	30.8 ± 7.5 years
IV	45	23/22	24/21	30.8 ± 7.4 years

Notes: N_{DYS} in Study I is the count of infants at risk of dyslexia, and in Studies II–IV adults with confirmed dyslexia. Age is denoted as mean $\pm$ SD. DYS – dyslexic or dyslexia risk group, CON – control group, f – female, m – male.

The participants or their parents gave their written informed consent to participate in the study. All experimental procedures were approved by the Ethics Committee for Gynaecology and Obstetrics, Pediatrics and Psychiatry of the Hospital District of Helsinki and Uusimaa (HUS) for Study I and by the HUS Coordinating Ethics Committee for Studies II, III and IV. All Studies were performed in concordance with the Declaration of Helsinki.

3.2 Experimental design and stimuli

All Studies I–IV were designed to compare neural measures between participants with dyslexia or its risk and neurotypical controls. An overview of the experimental procedure of all Studies is presented in Figure 3. Studies I–III investigated neural responses to speech or speech-sound stimuli, and Study IV the neuroanatomy. Neuropsychological test batteries were used to assess reading and reading-related skills of the participants or parents of the participants (Figure 3).

During the neurophysiological measurement (EEG in Study I or MEG in Study II), participants listened to a repeating Finnish-sounding pseudoword

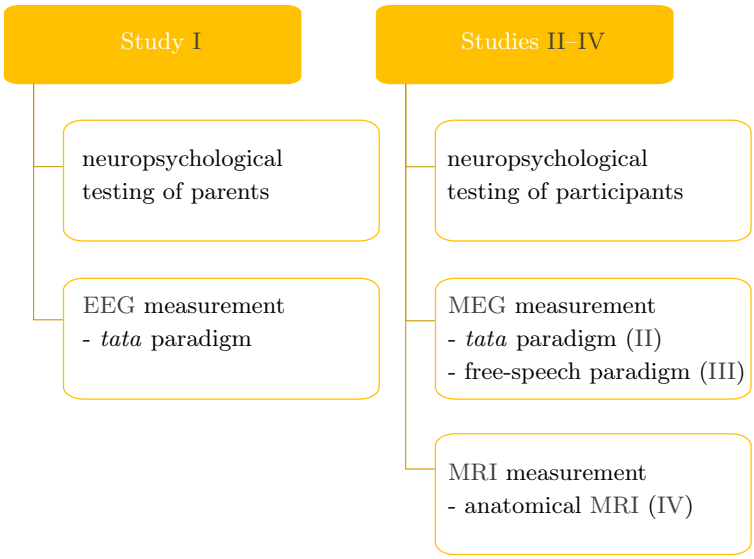

Figure 3: *Experimental procedure for all Studies. EEG – electroencephalography, MEG – magnetoencephalography, MRI – magnetic resonance imaging.*

/tata/ and occasional deviations of it which occurred always in the second syllable [Figure 4, first used by Pakarinen et al. 255]. The standard stimulus had a total duration of 300 ms with an onset of the second syllable at ≈168 ms, and the second */a/* at ≈181 ms. The deviations were in frequency (increase of fundamental frequency, $F0$, by 5 semitones from 175 Hz to 225 Hz), duration (extension of final */a/* by 87 ms), or vowel (*/tato/* with natural recording of the second syllable, $F0$- and duration-controlled). All deviations were created by editing the original *tata* sound file (Adobe Audition CS6, 5.0, Build 708 and Praat 5.4.01). The sound intensity level of all deviations was root-mean-square normalized to match the average intensity level of the original sound file.

The *tata* paradigm was presented as an auditory mismatch paradigm with frequently presented standard pseudowords and rarely occurring deviants in frequency, duration, and vowel (Table 5). A deviant was always followed by a standard, and the three deviants were presented with equal probabilities.

MEG data for Study III were collected after the *tata* paradigm of Study II

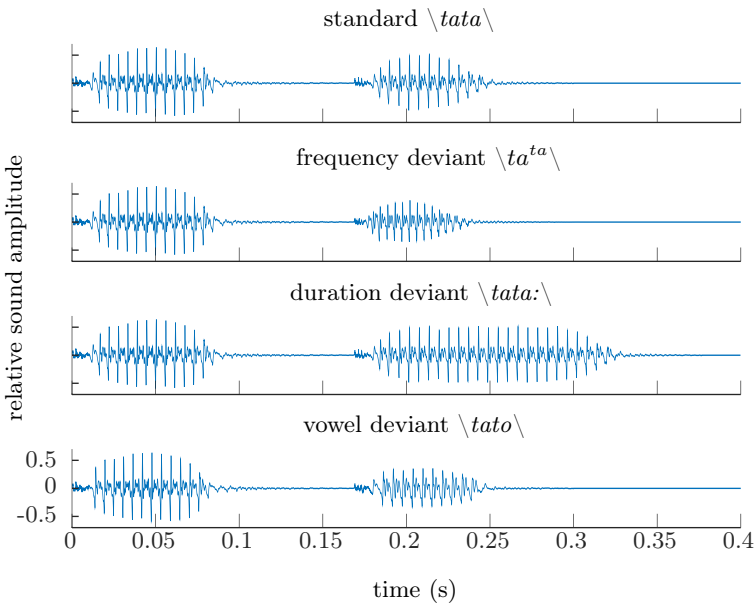

Figure 4: *Waveforms of stimuli used in* tata *paradigm.*

Table 5: Tata *paradigm parameters of infant Study I and adult Study II.*

Parameter	*Study I*	*Study II*
standard [%]	70.10	75.26
deviants [%]	25.30	24.74
each deviant [%]	8.43	8.25
novel* [%]	4.50	0.00
SOA [ms]	900 ± 50	800 ± 50

Note: *Responses to novel stimuli were not included in the analysis. SOA – stimulus-onset asynchrony.

from adult participants while listening to Finnish natural speech (Figure 3). The speech stimulus consisted of self-recorded material, such as small talk, reading of a book chapter, exchange of travel experiences, asking for directions, and excerpts from the Finnish national radio broadcast *Yle*, such as news and a podcast. The total duration of the speech stimulus was ≈10 min. Anatomical MRIs were obtained for Studies II–IV.

3.3 Data acquisition

3.3.1 Neuropsychological tests

Parents of infants in Study I with suspected dyslexia were tested with reading and writing tests of Nevala et al. [252] to confirm and assess the severity of their dyslexia (Table 6). The adult participants (Studies II–IV) were evaluated with a more extensive battery of neuropsychological tests to obtain a comprehensive profile of reading and reading-related skills (Table 6). The neuropsychological domains encompassed phonological processing, technical reading, working memory, and IQ. For the tests that were used to assess dyslexia [252, marked by asterisks in Table 6], age-matched standardized control data was used as normative data [28, 256].

Neuropsychological composite scores were formed by converting the scores of single tests into standardized z-scores, and averaging them for the domains of phonological processing and technical reading, separately for each participant (Table 6). The composites were formed based on classifications from previous theoretical and factor-analytic studies [28, 257–259]. For working memory, the standardized scores of subtests on number series and visual series were averaged according to instruction for the working memory component in Wechsler Memory Scale (third edition) (WMS-III) [260].

3.3.2 EEG/MEG data acquisition

EEG from newborn infants in Study I was recorded in Jorvi Hospital, Espoo, and the University of Jyväskylä, Jyväskylä, both in Finland. EEG was recorded with 18 active electrodes placed on an ActiCap according to the international 10/20 system with a QuickAmp amplifier (both: Brain Products GmbH, Gilching, Germany) at a sampling rate of 500 Hz. The online reference was an average of all electrodes.

EEG was recorded while infants were lying on their back in a crib. Sounds were presented with Presentation 17.2 Software (Neurobehavioural Systems Ltd., Berkeley, CA, USA) via a Genelec loudspeaker with 65 dB sound pres-

Table 6: *Overview of neuropsychological tests and composites.*

Comp.	*Single test*	*Variable(s) of interest*	*Description (The task was to...)*	*Reference*
Phonological processing	Pig Latin	acc	change the first syllables between two pseudowords (e.g., *kouta – mesi* rebuilds to *meuta – kosi*)	[252]
	Nonword span length	acc	repeat a sequence of consonant-vowel-consonant-vowel nonwords, the longest sequence of repeated nonwords (span) was recorded	[261]
	Rapid alternate stimulus naming	sp of second trial	name different changing stimuli (colours, numbers, letters) fast and accurately	[262]
Technical reading	*Word list reading	sp, acc	read a list of real Finnish words with increasing length as accurately and fast as possible	[252]
	*Pseudoword list reading	sp, acc	read a list of Finnish-sounding pseudowords with increasing length as accurately and fast as possible	[252]
Working memory	Number series	acc	recall digits of a series with increasing length, for forward span in the same order as presented, for backward span in the reverse order	WMS-III [260]
	Visual series	acc	touch the numbers on the board in the same order as instructor, increasing length of series	WMS-III [260]
Full IQ	Similarities	acc	describe the commonality between the two words	WAIS-IV [254]
	Vocabulary	acc	describe words freely	WAIS-IV [254]
	Block design	combined sp and acc	replicate a design by reformation of two-coloured blocks	WAIS-IV [254]
	Matrix reasoning	acc	decide the logical following pattern of a series of figures with the last element missing	WAIS-IV [254]
Not part of a composite score	†*Writing	sp	write text as fast as possible	[252]
	*Text reading	sp, acc	read an excerpt of real Finnish text as accurately and fast as possible	[252]

Notes: *Subtests used to evaluate dyslexia. †This test was only used in Study I. Comp. – Composite score, acc – accuracy, sp – speed

sure level (SPL).

Combined EEG (not reported here) and MEG for Studies II and III were recorded from adults at BioMag Laboratory in Helsinki University Hospital. MEG was recorded with an Elekta Neuromag Triux MEG system (MEGIN Oy, Helsinki, Finland) comprising 204 planar gradiometers and 102 magnetometers. The signals were online-filtered at 0.03–330 Hz and sampled at 1000 Hz. Both vertical and horizontal electrooculograms (EOGs) were recorded to identify eye movements. Head movements were tracked with head position indicator (HPI) coils throughout the recording. Digital marker points were measured before the recording by digitizing the HPI-coil positions as well as additional EEG-electrode positions with an Isotrak 3D-digitizer (Polhemus Inc., Colchester, USA) for co-registration of the head position in the MEG device and anatomical MRIs.

During all MEG recordings, adults were seated in an upright position and were instructed to keep their head still. They were further instructed to ignore the sounds while they watched a silenced, subtitled movie during the recording (Study II) or to listen to the speech while keeping their eyes open (Study III). The auditory stimuli were presented with Presentation Software via earphones with plastic tubes to both ears at a comfortable sound level (≈70–80 dB SPL).

3.3.3 MRI data acquisition

Anatomical MRIs were obtained from the adult participants in Studies II–IV at the Advanced Magnetic Imaging Centre at Aalto University, Espoo, Finland. High-resolution T1-weighted images were taken with a 3 T MAGNETOM Skyra MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. In total, 176 slices with a slice thickness of 1 mm, voxel size of $(1 \times 1 \times 1)\,\mathrm{mm}^3$ and field of view of $(256 \times 256)\,\mathrm{mm}^2$ were imaged with a magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence. All images were checked for incidental findings by a physician.

3.4 Data analysis

Infant EEG data (Study I) were mainly processed with Matlab Release 2015a and 2017a (The MathWorks Inc., Natick, Massachusetts, USA) and EEGlab toolbox 13.5.4b [263] with the custom-made CBRUPlugin2.0b (Tommi Makkonen, Cognitive Brain Research Unit, University of Helsinki). MEG data were mainly processed using the MNE-Python software package version 0.17.dev0 [264, 265]) and Matlab Release 2017a.

MRI data in Studies II and III was used for coregistration with the MEG data to improve source localization. It was pre-processed using Freesurfer software versions 5.3 and 6.0 [Martinos Center for Biomedical Imaging, 266–268]. In Study IV, MRIs were used for VBM analysis [212] with Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, UCL) with Matlab Release R2014b.

Statistical analysis for all Studies was carried out using SPSS versions 24.0 and 25.0 (IBM Corp, 2016, 2017, Armonk, NY, USA), R version 3.5.0 [269], RStudio version 1.1.453 [270], MNE Python version 0.17.dev0, SPM8, and Matlab (all above versions). Data processing scripts for Studies II and III are freely available at Github.

3.4.1 Pre-processing

The data pre-processing steps for all Studies are summarized in Tables 7 and 8. EEG and MEG signals had some common pre-processing steps and some method-specific steps (Table 7). Filters were applied differently for each Study; EEG data of Study I and MEG data of Study II were filtered with finite impulse response filters between 0.5–25 Hz and 0.5–30 Hz, respectively. MEG data of Study III was band-pass filtered into six frequency bands with a third-order Butterworth filter in forward direction. The six frequency bands had following cut-off frequencies: delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–12 Hz, beta 12–25 Hz, low gamma 25–45 Hz, and high gamma 55–90 Hz.

Table 7: *Pre-processing steps of EEG (Study I) and MEG (Studies II and III) data.*

Pre-processing step	*Study I*	*Studies II and III*
marking of noisy channels by visual inspection	x	x
removal of external magnetic interference with tSSS [271]		x
interpolation of noisy channels (max. ten)		x
compensation for head movements tracked with continuous HPI		x
removal of eye-movement and heart-beat artifacts with SSP [272, 273]		x
filtering	x	x
re-referencing to an average of mastoids or electrodes close to mastoids (P7 and P8), if mastoids were marked as bad	x	

Notes: tSSS – temporal signal-space separation, HPI – head position indicator, SSP – signal-space projection.

Anatomical MRI pre-processing steps of Studies II–IV are summarized in Table 8. Pre-processing steps in Studies II and III were the same, while they slightly differed in Study IV. Different methods were used for the segmentation of grey and white matter, as well as intensity normalization/modulation. In Studies II and III, the segmentation was part of the automated Freesurfer processing pipeline [274, 275] and manual adjustments were executed when non-brain matter was falsely classified as brain matter, as well as during intensity normalization, when white matter was falsely classified as grey matter. In Study IV, segmentation into grey matter, white matter, and cerebrospinal fluid was done by Unified Segmentation [276] with medium regularization. Segmented images were normalized to the common Montreal Neurological Institute and Hospital (MNI) brain template, while original image intensities were preserved by using modulation.

Table 8: *Pre-processing steps of MRI data.*

Pre-processing step	*Studies II and III*	*Study IV*
reorientation of anatomical T1 images		x
segmentation of brain and non-brain matter with Watershed algorithm [277]	x	
intensity normalization [278] and modulation	x	x
segmentation of grey and white matter	x	x
cortical parcellation [279–281]	x	
inflation [267]	x	
normalization to MNI brain template		x
smoothing of grey matter and white matter probability maps by spatial filtering		x

Notes: MNI – Montreal Neurological Institute and Hospital.

3.4.2 ERP/ERF analysis (Studies I and II)

The continuous data were divided into epochs of 100 ms before and 840 ms after stimulus onset for each stimulus type (standard, frequency, duration, vowel). Infant EEG data (Study I) were baseline-corrected at −100–0 ms prior to stimulus onset. Epochs were averaged separately for each stimulus type and participant and epochs with values exceeding pre-set thresholds were excluded from the averages. For infant EEG data (Study I), the threshold was ±120 µV for electrodes close to the eyes (Fp1, Fp2) and additionally, for all electrodes with data drifting more than 80 µV within an epoch, and extreme outliers (more than 3 *SD* from the mean of the individual participant's average for each stimulus type) were excluded from further analysis. Channel regions of interest (ROIs) were formed for frontal (F3, Fz, F4), central (C3, Cz, C4), left- (F3, C3), and right-hemispheric (F4, C4) areas on the scalp. For MEG data (Study II), the thresholds were 4 pT in magnetometers, 4 pT cm^{-1} in gradiometers and 250 µV in EOG channels. Deviant-minus-standard subtraction curves for both EEG and MEG data were computed separately for each deviant type and used for further analysis. For MEG data, the noise covariance was obtained from the pre-

stimulus baseline pooled together for all stimulus types, separately for each participant.

3.4.3 MMF source localization (Study II)

Anatomical MRIs and MEG coordinate systems were coregistered using the digitized fiducials and additional head points using the standard procedure of coregistration in MNE Python. Minimum-norm estimation (MNE) was used to estimate the MMF sources [282]. The cortical surface was decimated into an octahedron comprising 4098 sources per hemisphere. A single-shell boundary-element model (BEM) was set up as a volume conductor. The MNE inverse operator was computed with fixed source orientations to only estimate the currents of dipoles normal to the cortical surface and depth-weighting was applied. A ROI was pre-defined to the bilateral auditory cortex as established by earlier MMN/MMF literature [40, 80, 111, 283]. Due to the corresponding brain area as labeled in Freesurfer software being rather large, the ROI was further specified. Specifically, a functional label was established that was based on the most consistent activity across participants within the larger Freesurfer label. For visualization and group analysis, the individual source estimates were morphed to a common average brain template (*fsaverage* from Freesurfer software), and group averages were calculated.

3.4.4 ISC analysis (Study III)

ISC analysis was carried out for continuous MEG data from the free-speech paradigm. First, the MEG signals were filtered to six frequency bands and a Hilbert transformation was applied to obtain the complex-valued analytical signals. These signals were low-pass filtered at 0.3 Hz, downsampled to 10 Hz and projected into the previously set up octahedronal source space comprising 4098 sources per hemisphere. This projection was obtained using MNE [282]; the volume conductor was a single-shell BEM, noise covariance was estimated from a continuous 10 min MEG recording without the presence of a participant and pre-processed in the same way as described in Section 3.4.1, and depth-weighting was applied. Finally, the absolute value

of each source time series was taken. The resulting cortical amplitude envelope locations were morphed from the individual to a common average brain template (*fsaverage* by Freesurfer). Pair-wise Pearson correlations were computed for each subject pair at the corresponding source points in each frequency band. These pair-wise correlations were averaged for each group.

3.4.5 VBM analysis (Study IV)

Morphometric analysis was performed with VBM which is used to compare local (voxel-wise) grey- and white-matter concentrations between two groups [212]. For each participant, image volumes of grey matter and white matter were extracted for the whole brain.

3.4.6 Statistical analysis

Group comparisons were executed with repeated-measures analysis of variance (RM-ANOVA) in Studies I and II and independent-samples T-tests in Studies III and IV. The specific criteria are described Study-wise below. The significance threshold for all tests was set at 0.05, unless noted otherwise.

In Study I, MMR mean amplitudes were extracted in time windows with visually most prominent peaks, differently for each deviant. RM-ANOVAs with factors group (control/at-risk) and frontality (frontal/central ROIs) were run separately for each deviant and time window. Similar RM-ANOVAs were run with factor laterality (left/right ROIs) instead of frontality for each deviant and time window. Significant interactions were further investigated with *post-hoc* pairwise comparisons that were Bonferroni-corrected.

In Study II, maximal MMF source amplitudes were extracted in time windows with most prominent visual peaks. Three-way RM-ANOVAs were conducted to examine group and laterality effects and their interactions on MMF source amplitudes with the between-subjects factor group (control/dyslexic) and within-subjects factors laterality (left/right), deviant (fre-

quency, duration, vowel), and time (MMF, late MMF). Two-way RM-ANOVAs were conducted separately for the MMF and late MMF time windows to examine group and laterality effects and their interactions on MMF source latencies with the between-subjects factor group and within-subjects factors laterality and deviant. Main effects of deviant or time were not investigated. Greenhouse-Geisser corrections were applied in case of sphericity violations. Separate follow-up RM-ANOVAs were conducted for significant three-way interactions. *Post-hoc* pairwise comparisons with Bonferroni correction were conducted for significant two-way interaction effects. Partial Pearson correlations between left and right MMF source amplitudes and neuropsychological composites (Table 6), were calculated across both groups using performance IQ as a covariate, and separately for each group. Bonferroni correction was applied to account for multiple comparisons.

In Study III, ISC differences between groups (i.e., *control* > *dyslexic* and *control* < *dyslexic*) were tested separately for each frequency band with a permutation-based T-test. First, surrogate difference maps were created by permuting the subject labels 5000 times and then calculating the independent-samples T-tests [284]. Then, the independent-samples T-test was computed for the unpermuted ISCs between groups for each source location (20484 locations). Cluster correction was applied by identifying surrogate clusters based on spatial proximity for each of the 5000 surrogate maps, and returning the maximal cluster size for each map. The 5000 maximal cluster sizes represented the null distribution of cluster sizes. In order to control for all comparisons across all frequency bands (six), the maximum statistics approach was applied [285] by using the maximum of all six null distributions as a cutoff for the ISC contrast. Maximal absolute T-values were collected from the largest clusters with ISC differences and MNI coordinates were mapped to the automated anatomical labeling (AAL) brain areas [286]. For the correlational analysis between ISC in each frequency band and neuropsychological composite scores, the Mantel test was utilized [287]. For each neuropsychological composite (Table 6), regression matrices were modeled by averaging the test scores between each subject pair. The Mantel test was performed as Spearman rank correlation between ISC and regression matrices for each composite. Surrogate maps were computed by permuting subject labels 5000 times. The following steps were similar to the previous ISC difference map computation, i.e., cluster correction, formation

of null distribution by returning maximal cluster sizes, application of maximum statistics. For both analyses, only clusters larger than the cutoff size were visualized.

In Study IV, the extracted whole-brain grey-matter and white-matter volumes were compared between groups with independent-samples T-tests considering both contrasts (*control* > *dyslexic* and *dyslexic* > *control*). For all VBM analyses, the nuisance covariates age, gender, and total intracranial volume were used, as well as full IQ. The whole-brain uncorrected threshold was $p < 0.005$ and a family-wise error rate corrected $p < 0.05$ was applied for each cluster with a minimal voxel count of 100. Additional correction for nonstationarity was applied [288]. The AAL was used to identify the significant anatomical regions [286]. Correlations between grey-matter and white-matter volumes and reading-relevant skills were evaluated with one-sample T-tests for each neuropsychological composite (Table 6) across both groups. Partial Pearson correlations with previously mentioned covariates were calculated between significant clusters from the one-sample T-tests and each corresponding neuropsychological composite. Corrections for multiple comparisons were addressed with false discovery rate.

4 Summaries of the Studies

4.1 Neural speech discrimination in newborns at a high or low risk of dyslexia (I)

Genetic risk factors related to dyslexia can be best studied at early developmental stages, due to minimal environmental exposure. Newborn infants are able to neurally process auditory stimuli and detect subtle changes in speech sounds. As abnormal neural speech-sound processing has been related to dyslexia, it is important to evaluate whether these deficiencies are evident already in infants at elevated risk. This study addressed how an elevated familial risk of dyslexia is reflected in neural discrimination of speech sounds in newborn infants.

Eighty-eight newborns participated in the Study. Half of them had a parent with confirmed moderate to severe dyslexia (at-risk group) and the other half did not have close relatives with dyslexia or other language disorders (control group). Their MMRs were extracted from EEG to frequency, duration, and vowel changes in pseudowords and compared between the at-risk and control group. The main hypothesis was that at-risk newborns have absent or diminished MMRs to speech-sound changes.

MMRs to speech-sound changes were atypical in newborns that had an elevated familial risk of dyslexia (Figure 5, left, Table 9). Early negative MMRs were found to duration and frequency deviants in the control group, but they were absent in the at-risk group. A comparison of the MMR amplitudes between groups yielded a diminished early negative MMR to duration changes in the at-risk group (Table 9). These results suggest that at-risk infants could not discriminate duration and frequency changes at the early processing stage (≈90–100 ms after deviance onset). Furthermore, positive MMRs at later processing stages (from ≈300 ms after deviance onset onwards) were elicited by all three speech-sound deviants in both

groups, except by the frequency deviant in the control group. Positive late MMRs did not significantly differ in amplitudes between the groups (Table 9).

Infants at familial risk of dyslexia showed abnormal neural responses to speech-sound changes. The absence of the early negative MMR (to frequency and duration changes) and presence of a late positive MMR (to frequency changes) in at-risk infants could indicate less mature neural auditory processing [289]. These atypicalities at a very early developmental stage can lead to difficulties in phonological processing that are thought to be the main cause of dyslexia [4, 35–37]. Follow-up analyses should investigate how these atypical neural responses in newborns are related to pre-reading and reading skills, as well as dyslexia diagnosis in the future.

4.2 Neural speech discrimination in adult dyslexic and typical readers and its association with reading-relevant skills (II)

Poor speech discrimination has been associated with dyslexia, and may represent poor phonological representations in the brain, according to the phonological deficit theory. Yet, only few studies have investigated neural speech discrimination in dyslexic adults, and even fewer have characterized the neuromagnetic sources. This Study aimed to investigate whether neural MMF sources during speech-sound discrimination differ between adult dyslexic and typical readers in strength and laterality, and to find out whether the source strengths are associated with reading-related skills.

Forty-three healthy adults, of which half had dyslexia participated in the Study. Their MEG was collected during passive listening to a stream of pseudowords and changes embedded in them (same paradigm as in Study I), and anatomical MRIs were obtained to improve source localization. The MMF source strengths and lateralities were compared between groups, and correlated with reading-relevant skills, i.e., technical reading, phonological processing, and working memory skills. The main hypotheses were that adults with dyslexia have weaker MMF source strengths to speech-sound

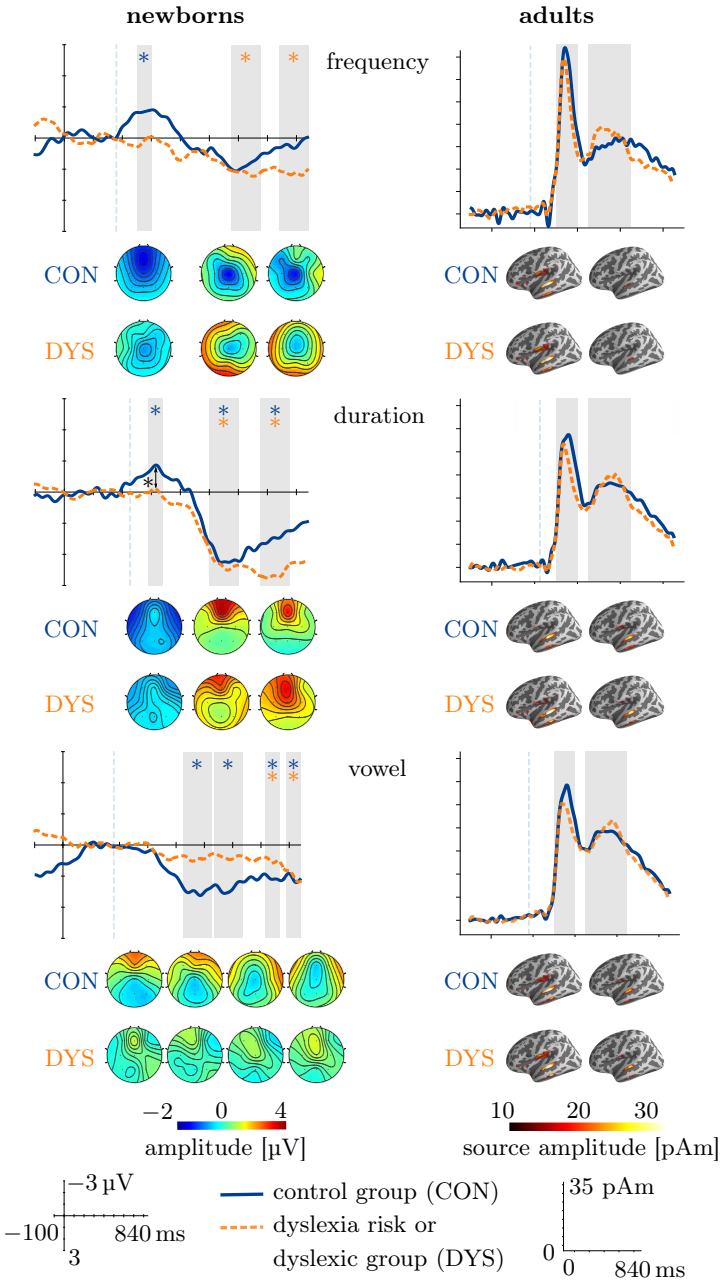

Figure 5: *Newborn mismatch responses (MMRs) (left, Study I, frontal electrodes) and adult source mismatch fields (right, Study II, left hemisphere) to speech-sound changes. Vertical grey dotted lines represent change onsets and shaded areas time windows analyzed. Significant newborn MMRs (left) are marked with asterisks in the corresponding group colour, the group difference is marked with a black asterisk. Approximately below each time window, the scalp maps (left) and source distributions (right) are visualized.*

Table 9: *Significant repeated-measures analysis of variance (RM-ANOVA) results of newborn mismatch responses (MMRs) and adult mismatch fields (MMFs) to speech-sound changes.*

	RM-ANOVA				Post-hoc *comparisons*		
TW	*effect*	$F(df1, df2)$	p	η_p^2	*effect*	MD	p
Study I: infant MMRs							
DUR							
early neg. MMR	group	4.54 (1, 74)	.036	.06	DYS < CON	0.750 µV	
VOW							
late pos. MMR	laterality x group	4.41 (1, 65)	.040	.06	right: DYS < CON	−1.283 µV	.057
					CON: left < right	−0.860 µV	.019
Study II: adult MMFs							
AMPLITUDES							
MMF &	laterality	9.48 (1, 41)	.004	.19	left > right	8 pAm	
late MMF	laterality x deviant	5.44 (2, 82)	.006	.12	see three-way interaction		
	laterality x deviant x time	4.75 (2, 82)	.011	.10	separate RM-ANOVAs for the two TWs		
MMF	laterality	6.89 (1, 41)	.024	.14	left > right	8 pAm	
	laterality x deviant	7.91 (2, 82)	.001	.16	VOW: left > right	14 pAm	<.001
late MMF	laterality	9.41 (1, 41)	.008	.19	left > right	9 pAm	.004
LATENCIES							
late MMF	laterality x group	4.46 (1, 41)	.041	.10	CON: left > right	29 ms	.010

Notes: TW – time window, η_p^2 – effect size, MD – mean difference, CON – control group, DYS – dyslexic or dyslexia-risk group, DUR – duration deviant, VOW – vowel deviant, pos. – positive, neg. – negative.

changes and that the MMF source strengths correlate with the three selected reading-relevant skills.

Two neural MMF source responses, the MMF (125–180 ms after deviance onset) and the late MMF (375–420 ms) were elicited in the bilateral auditory cortices. They did not differ in strength or laterality between typical and dyslexic readers (Figure 5, right, Table 9). Speech-sound discrimination in both groups was left-lateralized, both the MMF to the vowel deviant and the late MMF across the three deviants (Table 9). The neuropsychological test profile shows that in addition to the technical reading score which was part of the dyslexia criteria (Section 3.1, Table 6), controls outperformed dyslexics also in phonological processing and working memory tests (Figure 6). Better verbal working memory skills across groups were associated with stronger MMF sources in the left hemisphere, specifically to the duration deviant (Table 10). In the dyslexic group, better technical reading skills were associated with stronger late MMF sources in the right hemisphere.

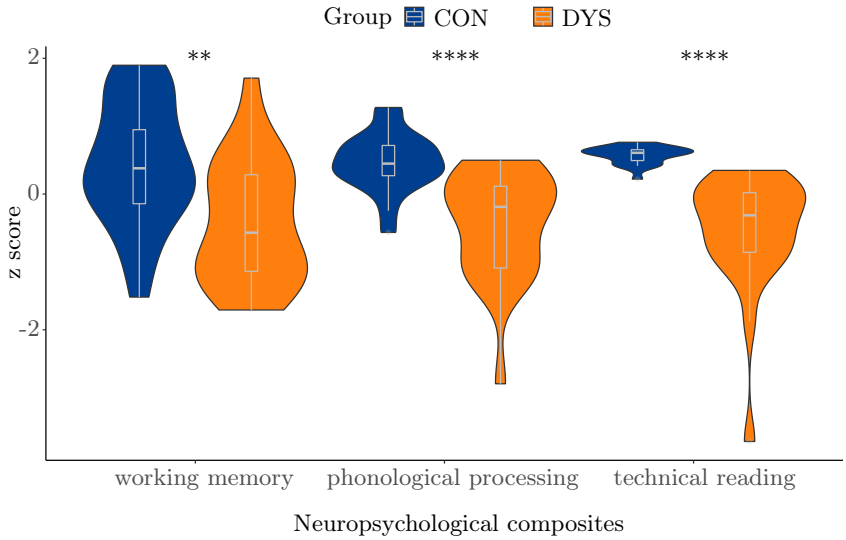

Figure 6: *Distributions of reading-relevant skills of adult dyslexic (DYS, orange) and typical readers (CON, blue) in Studies II–IV depicted as violin plots (colour) and box plots (light grey). Asterisks indicate levels of significance from comparing groups with Wilcoxon test; **$p < .01$, ****$p < .0001$.*

Table 10: *Correlations (r) of reading and related skills with functional and anatomical brain measures.*

Reading-relevant skill	*Brain measure*	*Brain area of peak correlation (Brodmann area)*	*r*	*p*
Study II: Partial Pearson correlations controlling for performance IQ. Only Bonferroni-corrected findings are listed.				
WM	L MMF to COMB	L mid. temporal (21, 22)	.25	.030
WM	L MMF to DUR	L mid. temporal (21, 22)	.40	.024
verbal WM	L MMF to DUR	L mid. temporal (21, 22)	.46	.006
WM	L MMF to COMB (only CON)	L mid. temporal (21, 22)	.37	.015
TR	R late MMF to COMB (only DYS)	R sup. temporal (41, 22)	.36	.028
Study III: Spearman rank correlation (Mantel test). Only peak values in significant frequency bands are listed.				
PP	ISC in delta band	L supramarginal (40)	.24	$< .001$
PP	ISC in theta band	R mid. temporal (19)	.25	$< .001$
PP	ISC in alpha band	L precuneus (7)	.15	$< .001$
PP	ISC in beta band	R postcentral (1)	.29	$< .001$
PP	ISC in high-gamma band	L sup. frontal (10)	.26	$< .001$
TR	ISC in delta band	L precuneus (30)	.18	$< .001$
TR	ISC in alpha band	R anterior cingulate (32)	.18	$< .001$
TR	ISC in low-gamma band	L fusiform (19)	-.28	$< .001$
WM	ISC in delta band	R sup. frontal (9)	.15	$< .001$
Study IV: Partial Pearson correlations controlling for age, sex, total intracranial volume and full IQ.				
TR	grey-matter volume	L sup. temporal (38)	.63	$< .001$
TR	white-matter volume	R putamen	.61	$< .001$
WM	white-matter volume	brainstem	.52	.001

Notes: Correlations including all participants are reported, unless noted otherwise. WM – working memory, TR – technical reading, PP – phonological processing, L – left, R – right, MMF – mismatch field, COMB – all deviants combined (duration, frequency, vowel deviants), DUR – duration deviant, CON – control group, DYS – dyslexic group, ISC – inter-subject correlation, mid. –middle, sup. – superior.

Comparable neuromagnetic source strengths during speech discrimination in dyslexic and typical readers might suggest that the dyslexic group did not have deficits in phonological representations, in line with an elaboration of the phonological deficit theory [39, 40]. However, the associations between MMF source strengths and technical reading, as well as working memory indicate that poor speech discrimination is connected with reading and working memory problems.

4.3 ISC between adult dyslexic and typical readers during listening to natural speech (III)

Speech processing impairments are evident in dyslexia and could appear due to deficits in temporal sampling of the speech signal. Previous studies addressing these deficits have scarcely used real-life speech as stimuli. ISC can be used to analyze neural responses to real-life speech, but has not been used to address possible speech processing deficiencies in dyslexia. Addressing this gap, this Study used ISC for the first time with MEG to find out whether cortical activity during listening to real-life speech is atypically synchronized between dyslexic readers. It further aimed to investigate the relationship between ISC and reading-relevant skills.

MEG was recorded from 44 participants (same as in Study II) while they listened to natural Finnish speech. ISCs of the neuromagnetic signals were computed separately between dyslexic and typical adult readers. Correlations between reading-relevant tests (same as in Study II) and ISCs were obtained across both groups. Based on the temporal sampling deficit theory [45], reduced ISCs in low (delta, theta) frequency bands and enhanced ISCs in higher (gamma) frequency bands were expected in dyslexic readers. Additionally, correlations of ISCs with reading-related skills were expected.

ISCs differed between dyslexic and typical adult readers during listening to natural speech. Compared to typical readers, ISC was weaker in dyslexic readers in delta and high gamma bands, while it was stronger in the theta, beta and low gamma bands (Figure 7), partly in line with the hypotheses. Reading-related skills were associated mostly positively with ISC; in five

frequency bands with phonological processing, in three bands with technical reading and in one band with working memory (Table 10).

Reduced ISC in the delta band in dyslexic readers could reflect inefficient temporal sampling of phrase boundaries from natural speech, supporting the temporal sampling deficit theory [45]. Enhanced ISC in the beta and low gamma bands in dyslexic readers, on the other hand, could be a sign of 'oversampling' [194]. The beta band corresponds to phoneme-rate information from speech, and its oversampling could lead to a working-memory overload, ending in slower and less efficient processes. This Study shows that ISC might be susceptible to several features in natural speech that could contribute to the problems in dyslexia. Furthermore, inter-individual differences in speech processing were related to reading-relevant skills, affirming a link between speech and reading networks in the brain.

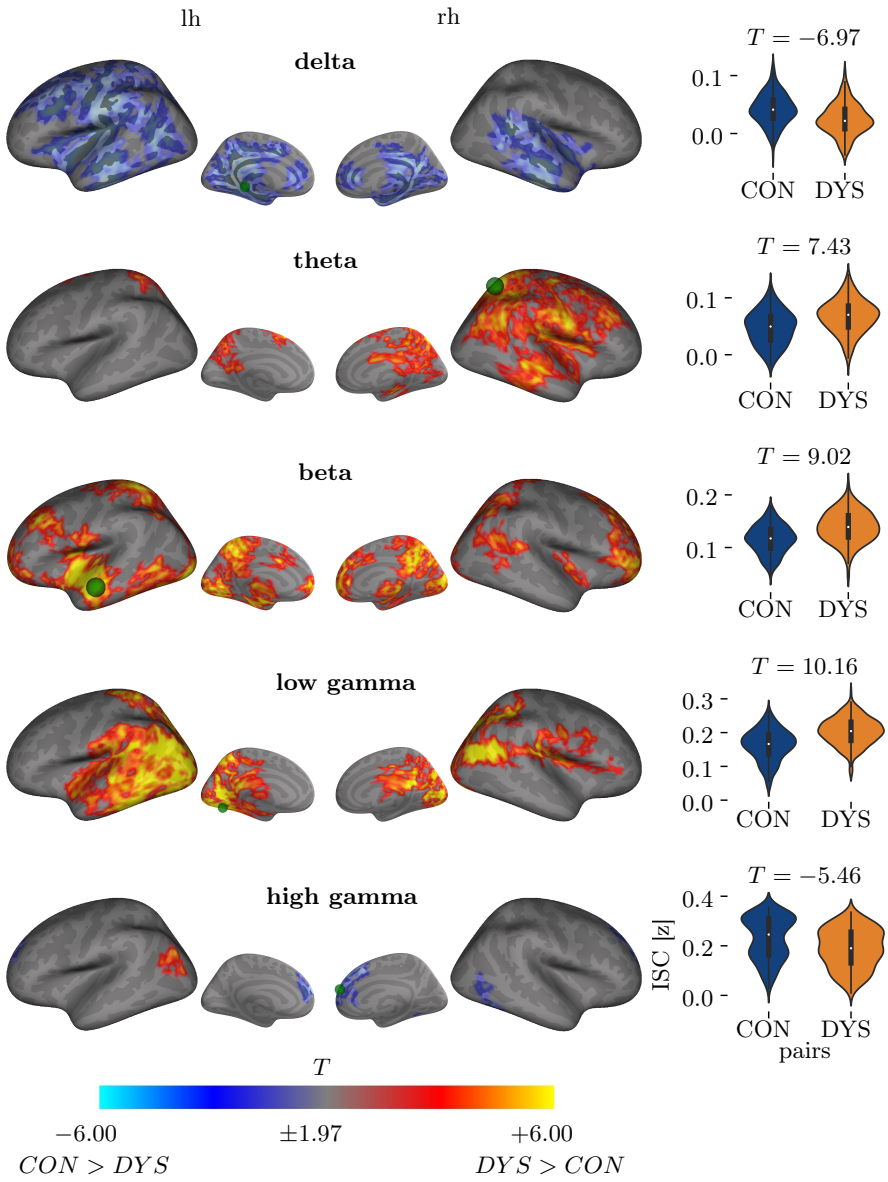

Figure 7: *Inter-subject correlation (ISC) differences between dyslexic (DYS) and control (CON) groups during listening to speech in different MEG frequency bands (Study III) on average brain surfaces (left). The peak ISC difference in the largest cluster is marked as a green dot (left) and the ISC distribution in DYS and CON pairs at the peak (green dot) is visualized as violin and box plot with the peak T value displayed above (right). lh – left hemisphere, rh –right hemisphere.*

4.4 Neuroanatomical correlates of dyslexia and reading-relevant skills (IV)

Structural abnormalities in the brain have been investigated in individuals with dyslexia for more than 40 years. Even though it is evident that such abnormalities exist in dyslexia, previous neuroanatomical studies on grey- and white-matter volumes in dyslexia have only reported few consistent findings. This Study contributes to the field by investigating structural brain abnormalities of adult dyslexic readers in a moderately sized and behaviourally well-characterized sample. In addition, it aimed to examine the association of brain structures with reading-relevant skills.

To that end, the anatomical MRIs of 45 participants (same sample as in Studies II and III), of which half had confirmed dyslexia, were analyzed with VBM to obtain whole-brain grey- and white-matter volumes. The hypotheses based on previous findings were that adults with dyslexia have a reduced total brain volume, reduced grey matter in left and right temporal areas, as well as the cerebellum, and reduced white matter in left temporo-parietal, bilateral frontal, left central, as well as right temporal and subcortical midline regions. Furthermore, it was hypothesized that reading-related skills correlate with grey- and white-matter volumes, in the same areas of group differences and to the same direction.

Grey-matter volume was decreased in dyslexic adults in a left-hemispheric cluster comprising STG, IFG, insula, hippocampus, amygdala, claustrum, putamen, globus pallidus, and subcallosal gyrus (Figure 8). White-matter volume was decreased in dyslexia in two right-hemispheric clusters comprising the middle temporal gyrus, hippocampus, and precuneus (Figure 8). These results are partly in line with the hypotheses. However, total brain volume was not reduced in the dyslexic group (both groups mean 1.3 l, SD 0.1 l, $p = .666$, independent-samples t-test). Grey- and white-matter volumes were further associated with reading-related scores across both groups (Table 10): Areas with reduced grey-matter volumes in dyslexia had an overlap with those positively associated with technical reading across groups, corroborating the group differences. Associations between technical reading and grey-matter volume were found in a left-hemispheric cluster

comprising STG, middle temporal gyrus, fusiform gyrus, insula, amygdala, parahippocampal gyrus, and hippocampus. Further associations in brain areas other than those showing group differences were found between better technical reading and larger white-matter volume in a large cluster comprising right insula, globus pallidus, putamen, IFG, precentral gyrus, bilateral parahippocampal areas, pons, and left cerebellum. Better working memory was correlated with larger white-matter volume in brainstem and bilateral cerebellum.

The atypical brain anatomy found in adult dyslexics is compatible with previous meta-analyses [132, 220, 221] and manifests in those areas that are especially important for reading [105]. The observed associations of better technical reading and larger grey-matter volume further support that these areas are relevant for reading, possibly as part of the neural reading network.

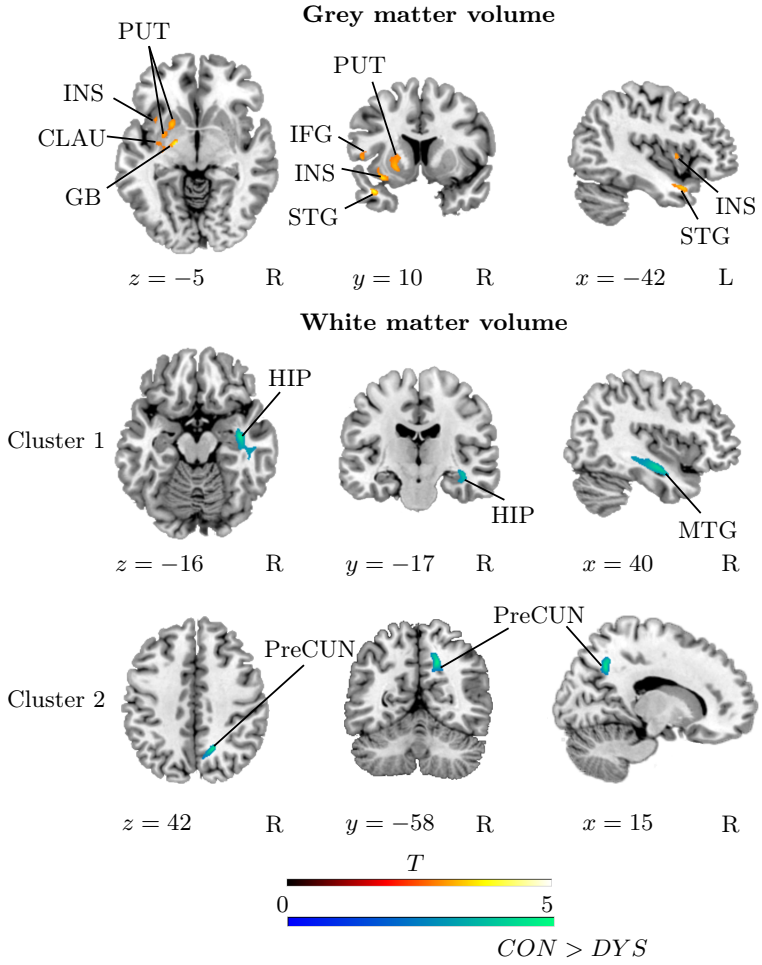

Figure 8: *Brain areas of grey- (top) and white-matter (bottom) decrease in dyslexic compared to typical readers (CON > DYS; Study IV). CLAU – claustrum, GB – globus pallidus, HIP – hippocampus, IFG – inferior frontal gyrus, INS – insula, L – left, MTG – middle temporal gyrus, PUT – putamen, R – right, STG – superior temporal gyrus, preCUN – precuneus.*

5 General discussion

Dyslexia is a learning disorder characterized by reading and writing difficulties. However, the neural underlying mechanisms are complex and multifactorial. This thesis aimed to shed light on selected neural functional mechanisms during speech discrimination and speech processing in dyslexia and its risk, tapping possible phonological and temporal sampling deficits. Additionally, anatomical correlates of dyslexia were investigated. It was further probed whether these functional and anatomical neural measures are related to reading-relevant skills.

The *first objective* of this thesis was to investigate neural speech-sound discrimination and its possible deficiencies in newborns at familial dyslexia risk and adults with dyslexia. Study I showed that newborns at high risk of dyslexia had atypical neural discrimination responses to speech-sound changes in pseudowords. In Study II, adults with dyslexia did not differ from typical readers in their neural discrimination responses to the same speech-sound changes.

Secondly, neural processing of natural speech was investigated in typical and dyslexic adult readers with ISC. In Study III, adults with dyslexia had weaker ISC in delta-, and high-gamma-frequency bands, and stronger ISC in theta-, beta-, and low-gamma-bands compared to typical readers.

The *third objective* was to examine the neuroanatomical correlates of dyslexia. Study IV found that dyslexic adults had reduced grey-matter volume in left-hemispheric fronto-temporal areas and subcortical structures, and reduced white-matter volume in right temporal areas and subcortical structures.

The *last objective* was to probe whether reading and reading-relevant skills are related to neural function during speech processing and to brain structures in typical and dyslexic adult readers. Such links were found in Studies II–IV. Technical reading and working memory skills were positively correlated with source strengths to speech-sound changes (Study II), with syn-

chronization strength in one or more frequency band(s) during listening to natural speech (Study III), and with grey- and/or white-matter volume bilaterally in the cortex and subcortical structures (Study IV). Phonological processing performance was positively associated with synchronization strength during listening to natural speech in five frequency bands (Study III).

5.1 Phonological deficits in dyslexia and its risk

5.1.1 Atypical speech discrimination in infants at risk of dyslexia

Study I of this thesis determined how an elevated risk of dyslexia is connected to speech discrimination deficits at birth. Whereas newborns without inherited dyslexia risk had early negative MMRs to duration and frequency deviants, they were absent in the at-risk group. Furthermore, early negative MMR amplitudes to duration deviants were diminished in at-risk infants. These results are in line with previous studies that have consistently shown absent or diminished MMRs in at-risk infants [137–140]. Compared to Study I, however, they used non-speech stimuli [140] or changes in consonants [137–139] instead of vowels, and older age groups [137–140]. Furthermore, all alertness levels (active sleep, quiet sleep, awake) were included in this Study, while others have, e.g., only used data from quiet sleep [138, 139]. This Study adds to the existing body of MMR dyslexia risk research in early infancy with a large sample size and a new speech-sound change type (vowels in pseudowords). The diminished or absent MMRs in at-risk infants to two out of three speech-sound changes suggest impaired neural speech discrimination in at-risk individuals already at birth, supporting previous work.

These atypical neural speech discrimination responses in at-risk newborns demonstrate that dyslexia risk can be identified with auditory MMRs at the group level long before any behavioural characterization of oral language development or reading instruction is possible. The MMR in infancy can therefore be seen as a neural marker of dyslexia risk. Together with a re-

cent meta-analysis [142], the results of Study I suggest that auditory ERPs can be relatively stable markers to distinguish between groups of infants at heightened risk of dyslexia and those at no risk. While the meta-analysis reported an overall large effect size (Hedge's $g = 0.715$) for mean ERP amplitude group differences (MMR and other ERP components) between at-risk and control infants across twelve infant dyslexia risk studies [142], the group effects in Study I are rather small to medium in size. This could be due to differences in stimuli (e.g., non-speech vs. speech), age of the infants, ERP components used in the analysis, and the definition of dyslexia risk. Regarding the latter point, in some studies of the meta-analysis, dyslexia risk was assessed retrospectively (based on whether children had reading difficulties when they were older) which might have lead to more homogeneous neural response characteristics in the at-risk groups. In Study I, dyslexia risk was based on assessments of parental dyslexia. It is noteworthy that the selection of at-risk infants in the present research was based on stricter criteria than in most other similar (non-retrospective) studies, i.e., at least one parent had to have moderate to severe dyslexia, defined by 2 SD below norm [instead of 1 SD as, e.g., in 137, 140] in two out of three reading and writing subtests [252, Section 3.1].

In addition to the absence of early negative MMRs, late positive MMRs were only elicited in at-risk infants (to the frequency deviant). MMRs of different polarities can co-occur during infancy [97, 290, 291], likely reflecting a stage of neural maturation of auditory discrimination. Early negative MMRs could indicate a more mature neural response, as it has been shown that the negative MMR becomes more prominent in older infants and children [85, 88–90, 289]. On the other hand, positive MMRs have been associated with immature, developing neural systems [85, 87–89]. Therefore, the current results suggest that at-risk infants could have a more immature neural system than controls that may lead to developmental delays in language and reading acquisition.

The early deficits and possible immaturity in at-risk infants as obtained in Study I further imply that the atypical discriminative responses could be a cause rather than a result of dyslexia. This is compatible with previously described differences between control and at-risk groups in neural structure and function, specifically auditory and phonological processing [for a review,

see 107]. Aberrant neural speech processing at this early developmental stage can have long-lasting effects. It can lead to a weak formation of speech-sound or phonological representations [phonological deficit theory, 4, 35–37] that are the basis for forming associations between letters and speech sounds, arguably the most critical step during reading (Sections 1.1.1 and 1.1.2). Longitudinal studies have shown that infant auditory MMRs/ERPs can predict later language development [140, 144, 155–157, 292–295], and a few specifically associated abnormal speech processing in at-risk infants with non-fluent reading later [156, 292, 293]. In conclusion, the current results might be connected to phonological deficits in dyslexia, which were proposed to underlie reading problems, supporting the phonological deficit theory [4, 35–37].

It is known that only about 40–60 % of the at-risk infants will develop reading difficulties as in dyslexia [147]. Interestingly, auditory ERPs of those typically developing at-risk infants can still be diminished as compared to typical readers at no risk, suggesting that auditory ERPs could rather indicate genetic risk than dyslexia itself [endophenotype, 15, 128, 294]. This suggestion has implications for the use of infant ERPs/MMRs as individual predictors for language development. While they have proven useful for prediction at group level (see above), the prediction accuracy at the individual level is not accurate enough, at least partly due to the high variability of infant ERPs/MMRs [86, 148]. As the goal of most research on dyslexia and its risk arguably is to provide targeted support to those at highest risk, it would be valuable to improve predictions at the individual level. However, the poor reliability of MMN in general [e.g., 296] and of MMRs in infants in particular still pose considerable challenges. At this point, MMRs can serve to characterize dyslexia risk, and in combination with genetic, neuroanatomical, prereading and reading, as well as other behavioural information, have the potential to improve prediction accuracy [107].

5.1.2 No evidence for atypical speech discrimination in adults with dyslexia

Study II investigated whether discrimination of the same pseudoword stimuli as in Study I is impaired also in adults with confirmed dyslexia. Neuromagnetic speech discrimination responses in Study II were comparable between adults with dyslexia and typical readers, in source amplitudes, latencies, as well as lateral distribution. The absent group differences are in contrast to some previous studies that have shown diminished speech-elicited MMNs or ERPs in adults and children with dyslexia [for a review, see 53], but in line with other studies that did not report group differences [113, 129]. They are also in contrast to findings of basic auditory processing deficits that are thought to be prevalent in at least some dyslexic adults and children [for a review, see 106]. For group comparisons of lateral distribution results are mixed [112, 135, 297]. However, the absent group differences in the laterality of MMFs in Study II corroborate the findings of a recent large-scale study suggesting no lateralization atypicalities in language impairments [297].

There are several possibilities why the dyslexic group in Study II did not exhibit abnormalities in neural speech discrimination. *First*, the results can be interpreted in the light of a recent elaboration [39, 40] of the phonological deficit theory [4, 30, 35–38, 298]. It proposes that dyslexics have intact phonological representations, but the access to them is impaired [39, 40]. The current results are compatible with that suggestion since MMN/MMF, particularly the temporal-lobe sources, could reflect phoneme representations [299]. The access of phonological representations, on the other hand, is required for the Pig Latin and rapid naming subtests of phonological processing used in this thesis, in which dyslexics underperformed. Studies with larger participant groups should revisit this question and determine whether some subgroups of dyslexics have primarily phonological or phonological access problems.

Secondly, the majority of the dyslexic sample of Study II might lack or have less severe auditory processing deficits [106]. This could be due to the criteria used to define dyslexia in adults (Studies II–IV) which was a below-norm performance of at least 1 SD in reading (speed or accuracy) in

at least two out of three subtests [252]. While these criteria were based on reading performance, other studies also required working memory and/or phonological problems [108, 110] or deficits in three instead of two reading tests [109] to be defined as dyslexic. However, even other adult studies had similar [112] or more liberal criteria [111, 123]. The current dyslexic sample includes less dyslexic individuals with severe reading problems and more with mild problems (Figure 6), and latter ones could in turn have less severe neural deficiencies in speech processing [135, in compensated dyslexics]. It has been suggested that auditory processing deficits get alleviated or compensated, at least in some individuals, in late childhood [300]. MMRs have, e.g., been shown to be reliable discriminative markers between at-risk and control groups of infants and young children [127, 142, non-speech and speech stimuli included], but are more heterogeneous in older children aged around 6–7 years, some studies showing diminished, and others even enhanced MMR/MMN amplitudes in the at-risk group [127]. Studies I and II of this thesis support a neural speech discrimination deficit in infants that is related to dyslexia risk, but do not support a similar deficit in adult dyslexics, in line with the proposal above.

Thirdly, it is possible that the stimulus contrasts used in Study II were not sensitive enough to probe the possible speech/auditory processing deficits in adult dyslexics. Dyslexics have relatively consistently been found to have problems in neurally discriminating small (around 100 Hz or less, or <10 %), but not large stimulus changes [108, for reviews, see 53, 106]. The change of ≈29 % in frequency in the present Study could be considered large and therefore easy to discriminate also for dyslexics. Dyslexics also have problems in discriminating consonant changes in speech, shown by diminished MMNs [e.g., 112, 301, 302] and a categorical phoneme perception deficit [meta-analysis 303]. Unlike vowel and vowel duration changes used in this Study, consonant changes are smaller and may require more rapid neural processing, which has been proposed to be challenging for dyslexics [e.g., 304]. Diminished MMNs to vowel changes in dyslexia or its risk have only been scarcely reported [121, 305]. In comparison to simple, relatively repetitive stimuli as in Study II, the aforementioned studies either investigated children [121] or presented the stimuli in a context with high acoustic variation in adults [305]. Therefore, it is possible that the stimulus differences used in the present Study were so large and/or presented in a too simple

context that also the dyslexics could discriminate them without increased effort [cf. 129, who found a similar absence of MMF group differences to speech stimuli in children]. More complex sound patterns as found in natural speech could more likely reveal neural speech processing deficits in dyslexia (Section 5.2).

Even though the results of the current thesis suggest no speech discrimination impairment in dyslexic adults, speech-elicited MMF source strengths were linked moderately strongly to reading-relevant skills [comparable to 108]. *Firstly*, late MMF source strengths in the right hemisphere were positively associated with technical reading skills only in dyslexics. The absence of correlations in the control group with technical reading skills could simply be a result of increased variance of technical reading skills in the dyslexic group as opposed to a ceiling effect in the control group (Figure 6). On the other hand, it could also mean that dyslexic adults have developed different, possibly compensatory, strategies for reading that are associated with right-hemispheric speech processing [135, 306].

Secondly, MMF source strengths in the left hemisphere were positively correlated with verbal working memory skills across all participants. This corroborates earlier findings of correlations between working memory and MMN in adult musicians and non-musicians [151], and with LDN in children at-risk of dyslexia and controls [153]. The findings further show the relevance of verbal working memory in efficient and accurate speech discrimination. Verbal working memory problems were also more evident in dyslexics than visual working memory problems in the sample of this thesis, supporting previous findings [307–309].

5.2 Temporal sampling deficits in dyslexia

ISC has rarely been applied in clinical populations before [310], and this is the first Study investigating ISC in dyslexia. The main objective of Study III was to compare ISC between groups of dyslexic and typical readers. The main findings were weaker ISCs in dyslexic readers in delta- and high-gamma-frequency bands, while stronger ISCs were found in dyslexics in the theta, beta, and low-gamma bands compared to typical readers.

Due to its nature, the interpretation of ISC results is less straightforward than, e.g., ERP results. ISC is generally thought to be stronger, the more structured the stimulus is over extended periods of time [e.g., 180, 311]. The concept of neural entrainment can aid the interpretation of the novel dyslexia ISC results from MEG data. Similarly to the current ISC study, speech entrainment studies compare neural activity in different frequency bands measured with MEG or EEG during a listening task. The stimuli can, however, be manipulated [such as with amplitude modulation, e.g., in 194, 196, 202, 204, 312], in contrast to the presently used real-life speech. Importantly, an open debate remains about what the so-called 'entrainment' truly reflects. Whereas stimulus-entrained activity could reflect a change of intrinsic oscillatory neural activity due to the rhythms in speech, it could also be that entrainment is caused by phase locking, as ERPs are repeatedly evoked by acoustic edges in the continuous stream of speech [for reviews and discussion, see 313–315]. These acoustic edges may be related to syllables, phonemes, phrase boundaries etc. in speech. To summarize, entrainment studies are highly related and relevant for the current ISC findings, but are not an identical measure: Entrainment studies measure how neural activity follows the speech rhythms, while ISC measures the extent of correlation of neural activity between individuals during listening to the same speech stimulus.

The current ISC results are mostly in line with temporal sampling deficits in dyslexia [45]. As hypothesized, dyslexic readers had weaker ISC in the delta band compared to typical readers. Neural activity in the delta-frequency range has been associated with processing of phrase boundaries during speech parsing [43, 168]. Reduced ISC in dyslexic readers in the delta band could therefore reflect inefficient temporal sampling of phrase boundaries from natural speech. Previous entrainment studies support these findings in the delta band, e.g., dyslexics had reduced entrainment to the speech envelope [197], poorer encoding of noise-vocoded speech [200], as well as atypical lateralization in phase locking to speech modulations [202] and delta oscillations to a natural audiovisual stimulus [198].

Stronger ISCs in dyslexic than typical readers in higher frequency bands, i.e., beta and low gamma bands, are in line with a proposal of oversampling of fast-rate information in speech in dyslexia due to higher than normal en-

trainment in dyslexic than control participants [194], although their results were found in a slightly higher frequency range than the one used here. Beta and gamma bands correspond to fast-rate information in speech, such as phonemes [168, 206, 207]. Oversampling of phoneme-rate information has previously also been associated with working-memory deficits [194], although in the current Study correlations with working-performance were only found in the delta band. A working memory overload caused by oversampling could subsequently slow down and reduce the efficiency of speech processing. The current findings are further supported by previously found enhanced synchronization measured with the auditory steady-state response (ASSR) to beta-band amplitude modulations in dyslexic children and adolescents [196, 312]. A more accurate sampling of phonemes in dyslexia supports the allophonic theory of dyslexia that predicts a better within-phonemic category discrimination in dyslexic individuals than in typical readers [301].

Stronger theta-band ISC in dyslexic readers were, on the other hand, unexpected, as it was against the predicted reduced temporal sampling in low frequency bands. The theta band has been suggested to parse syllables in natural speech [42, 43]. Stronger ISC in this band could therefore imply that syllable information is oversampled or parsed with increased effort in dyslexia, similarly to the oversampling of phoneme-rate information in beta and low gamma bands. In line with the present results, enhanced synchronization as in higher phase locking in dyslexic than typical readers has been found to theta-band rates previously [204].

Little is known about high gamma rates in speech processing. One study suggests that high gamma frequencies could sample phonemic-categorical information from speech [208]. The mainly reduced high-gamma ISC in the current Study in dyslexics could therefore reflect deficient categorical phoneme information processing of speech, in line with the categorical phoneme processing deficit theory of dyslexia [303]. However, also enhanced sampling of high-gamma-rate information from speech has previously been described in dyslexia [194].

ISCs correlated with phonological processing, technical reading, and working memory skills. These findings imply that neural processing of natural

speech is associated with reading-relevant skills investigated in this thesis. This supports the suggestion of temporal sampling deficits leading to or being related to phonological processing problems [44] that are evident in dyslexia. These problems might then further result in reading and working memory problems. However, the links established here are only correlational.

To summarize, these results suggest that dyslexics process natural speech atypically, as evidenced by different ISCs compared to typical readers. These atypicalities generally support the temporal sampling deficit theory, affecting the parsing of several natural speech features. Irregular neural speech parsing was further linked to worse phonological processing and worse technical reading skills. These results support atypical processing of natural speech in dyslexia with a novel method for analysis of brain activity during continuous, natural stimulation. Due to the novel method, these findings should be replicated in future research with the same and different analysis approaches.

5.3 Neuroanatomical abnormalities in dyslexia

Several neuroanatomical differences were found in grey- and white-matter volumes between typical and dyslexic readers (Study IV): Grey-matter volume was decreased in dyslexic adults in left-hemispheric areas comprising STG, IFG, insula, hippocampus, amygdala, putamen, globus pallidus, claustrum, and subcallosal gyrus. Also white-matter volume was decreased in dyslexia in the right middle temporal gyrus and hippocampus, as well as in the right precuneus. The total brain volume did not differ between dyslexic and typical readers in Study IV.

The results of total brain volume not differing between groups is in contrast to findings of a recent meta-analysis [211]. It is currently not well known what a reduced total brain volume could reflect, although it has been suggested to either be a result of genetic variants linked to dyslexia, or of disrupted neural development [211]. In this Study, importantly, the local structural abnormalities occured in dyslexics despite a comparable total brain volume to normal readers.

Superior temporal areas and IFG are important for semantic, phonological, and syntactic processing [for a review, see 316]. The found reduction of grey-matter volume in dyslexia in these areas is consistent with previous meta-analyses reporting reduced grey matter in left superior temporal areas [132, 220, 221] and reduced activation of left superior temporal areas and IFG during reading or phonological tasks in dyslexia [meta-analysis 317].

Also diminished grey-matter volume in the *insula* was consistent with a previous study in dyslexic children [214]. It is responsible for processing of stimulus salience and cognitive control [318]. It has shown increased activation after reading interventions that could be explained by a better detection of salient events [319].

Left-hemispheric grey-matter reductions in subcortical areas confirm findings of a volumetric study in adult dyslexic males [320]. The *hippocampus* is the main neural correlate for several aspects of memory [321]. Its reduced grey-matter volume in dyslexia could be associated with difficulties in memory formation, as especially short-term memory is impaired in some dyslexics [26]. However, we found no associations between working memory performance and hippocampus grey matter volume. Also the present right-hemispheric white-matter volume reductions in the hippocampus of the dyslexic group are in line with a previous report [229]. The *amygdala* is thought to be mainly responsible for emotional processing, especially fear, as well as motivation, memory and stimulus salience [322]. The left amygdala was found to be activated by verbal stimuli with negative and positive emotional connotations [323]. Both, the detection of salient events and short-term memory aid reading, being compatible with the present results of reduced grey-matter volume in the amygdala of the dyslexic group. The *putamen* is thought to be involved in motor sequences, and showed enhanced activation in the left compared to right hemisphere during reading out loud [324]. The reduced grey matter in the left putamen in dyslexics in the present Study could therefore be associated with problems in reading-related articulatory processes. Reduced grey matter in the subcallosal gyrus has been reported in children with dyslexia previously [325]. In conclusion, the aforementioned left-hemispheric subcortical areas are not entirely new to dyslexia research, nevertheless are not yet abundantly studied, rendering further studies with a focus on subcortical areas necessary.

Further findings of the present Study are reduced grey matter in dyslexic compared to typical readers in the claustrum, representing a region that was not previously reported to be atypical in dyslexia. The *claustrum* is not a well-known structure between the insula and striatum that is highly connected to other brain areas. This connectivity hints towards mainly integrative functions, such as saliency detection and attention [326]. Attention deficits are comorbid with dyslexia, or even associated with dyslexia [327]. Despite a screening for attention problems, i.e., a self-report for ADHD, some attention problems might have been overlooked in the current sample. Lower grey-matter volume in the claustrum could therefore be related to problems with stimulus salience, integration, and attention in dyslexia. These findings need to be confirmed in the future.

White-matter volume in *right temporal areas* has been less studied than in the left hemisphere. However, a decrease of white-matter volume in the right temporal areas, as in the present Study, has also been reported in at-risk children prior to reading onset and may therefore be genetically rather than environmentally driven [226, 227]. The same areas could also be related to difficulties in phonological processing, as two studies found increased activation in right temporal areas during a phonological task after an intervention including auditory processing and oral language tasks in dyslexic children [328] and after a phonological intervention in dyslexic adults [306].

White-matter volume in the current Study was also reduced in the *precuneus* in dyslexic adults which was previously found to have decreased white-matter volume in dyslexic children in the same location as in the current Study [329]. It has further been related to visual processes in reading [330], suggesting that it is relevant for the visuo-attentional reading processes that can be affected in dyslexia.

The aforementioned processes are all closely or remotely related to the reading network, suggesting that the grey-matter reductions in dyslexia in these areas are associated with the reading deficit. This is in line with previous studies that have suggested several structural abnormalities in dyslexia in a mainly left-hemispheric network relevant for reading [for reviews, see 132, 220, 221]. It is further corroborated by correlations between brain

structure and technical reading in Study IV. Positive associations were found between technical reading and grey-matter volume in left-hemispheric areas that partly overlapped (comprising STG, insula, amygdala, and hippocampus) with the grey-matter volume reductions in the dyslexic group. Correlations between technical reading and white-matter volume were found in mainly right-hemispheric frontal and subcortical structures and left cerebellum. These results imply that the brain areas correlating with reading skills are part of the reading network, supported by previous functional neuroimaging findings during reading [317, 331]. The overlapping brain areas with correlations and grey-matter reductions in dyslexics suggest that structural abnormalities especially in these areas could be causally related to dyslexia, or a result of reduced reading exposure [cf. 248, 332, 333].

Interestingly, the cerebellum showed no abnormalities in grey- or white-matter volumes in dyslexia, in contrast to previous reports [132, 220, 221], but higher white-matter volume in the cerebellum correlated with technical reading and working memory skills. The role of the cerebellum in working memory and language functions is well established [334–338, for a review, see 339], and it is an important part of the reading network [340, 341, for a recent review, see 342]. In this Study, variances in grey- and white-matter volume of the cerebellum within the dyslexic group might have been too large to reach significant group difference effects. Additional correlations were found between white-matter volume in the brainstem and working memory. Auditory evoked brainstem responses were found to be dependent on working memory load previously [343]. The current findings strengthen the link between those structures and working memory skills.

In general, reduced volume in several structures of the dyslexic brain can be informative of two aspects: First, it could tell about the neurogenetic basis of functional deficits in dyslexia. Specific gene variants associated with dyslexia could contribute to the structural abnormalities [10, 224, 344]. These, in turn, can cause the functional deficits related to, e.g., reading and phonological processes that have been established by numerous studies and in this thesis. However, it is questionable how much contribution to brain anatomy in adults comes from genes. Therefore, the direct links from genes to cortical abnormalities in dyslexia remain to be established reliably [first approaches by, e.g., 345]. The second aspect that needs to be considered

are the environmental influences. Less reading exposure in dyslexia due to reading being difficult is another factor that contributes to shaping brain structures and can cause abnormal brain anatomy in dyslexia. Due to these two aspects being intertwined, neuroanatomical results highly depend on the selected sample, e.g., the specific reading profile, other related difficulties, and age.

5.4 Associations of anatomical and functional brain measures with reading-relevant skills

The associations between the neural functional and anatomical measures with reading-related skills in adults found in this thesis add to the scarce previous evidence of such associations in adults [108, 194, 195, 204]. The majority of correlations were obtained across both groups of typical and dyslexic readers and therefore indicate that reading and relevant skills are a continuum (Figure 6), in which dyslexia is defined by an arbitrary cut-off point. In this thesis, the definition of dyslexia was based on three reading tests (word, pseudoword, and text reading), of which two were included in the technical reading composite score. This score was a combined measure of word and pseudoword reading speed and accuracy (Table 6), tapping both lexical and sub-lexical processes of the reading network. This large overlap between the tests used for the group division into dyslexic vs. typical readers and those comprising the technical reading composite needs to be kept in mind when looking at the correlational results for the technical reading composite, as they are not independent from the group differences.

Technical reading was associated with speech discrimination, natural speech processing, and brain structures. The correlational results overlapped with the group differences, such that they indicated the same direction, e.g., less synchronized neural speech processing in dyslexia and less synchronized neural speech processing being correlated with worse technical reading scores (Section 5.2) or grey-matter volume reductions in dyslexia and reduction of grey matter being correlated with worse technical reading scores (Section 5.3), as expected. The correlations thus support the group differences, and add details on variance of reading ability within groups, and the

monotonic to linear nature of the relationship between neural measures and reading.

Correlations between technical reading and natural speech processing were found in overlapping brain areas with correlations between technical reading and brain structures, i.e., technical reading was associated with functional and anatomical neural measures in the same brain areas. The overlaps were found between ISCs in the delta and low gamma bands and grey-matter volumes in the left temporal areas, such as middle and superior temporal gyri. The same areas also indicated group differences in both ISCs and grey-matter volumes. Even though in this thesis, only the right-hemispheric late MMF was correlated with technical reading, in general the MMF and late MMF were generated in bilateral temporal cortices. These overlaps imply the relevance of both function and structure in especially left-hemispheric temporal areas for reading and reading deficiencies [38, 127, 131, 132, 142, 220, 221, 230, 317].

The associations between neural speech processing and reading functions may be based on an overlap of neural networks for reading and speech processing. Listening and speech processing are parts of the oral language network that develops early in life, and has even been suggested to be hard-wired in the brain [346]. The reading network, on the other hand, develops later in life and requires active teaching. It is thought to be constrained by the oral language network [346], which may explain the strong links of neural speech processing and reading-relevant skills in this thesis.

The *phonological processing* composite score was calculated from rapid naming skills, a phonological task (Pig Latin), and nonword span length (Table 6). Rapid naming skills were here and earlier [e.g., 28] considered to be the phonological naming part of phonological processing, but can also be seen separately [e.g., 347]. Furthermore, verbal working memory was here included in the working memory composite score, separately from phonological processing, while others have included it as part of phonological processing [for a review, see 19].

Phonological processing is strongly linked to reading skills, and phoneme awareness has been suggested to influence reading development causally [19]. In support of this suggestion, several functional neuroimaging studies,

utilizing fMRI, have found hypo- and hyperactivation in dyslexia during phonological tasks [e.g., 214, 348, for reviews, see 223, 317, 349]. Phonological processing is inherent to speech processing, as it deals with the sounds of language to analyze and understand words. The correlations in Study III between natural speech processing and phonological skills were therefore expected. Efficient neural processing when parsing the speech signal for distinguishing different sizes of phonological units has been suggested to directly affect the quality of phonological representations [44].

However, links were also expected between phonological processing and speech discrimination, as well as brain structure, but we did not obtain such links. This may be surprising as previous studies have proposed these links, e.g., phonological processing skills were correlated with MMN in children [117, 150] and with several anatomical measures [235, 242]. Possible reasons for no such correlation findings in this thesis could be the stimuli that are relatively easy to discriminate (Section 5.1.2), possibly not requiring phonological analysis. In addition, as discussed above, phonological processing skills can be also defined differently than in this Study. Furthermore, it is possible that the correlational effects are small, so that neither MMFs nor anatomical measures were sensitive enough to make them visible in a moderately sized sample.

Working memory was linked to speech discrimination, natural speech processing, as well as brain structures. The working memory composite score was formed from a verbal and visual working memory task, according to WMS-III [260]. Working memory is relevant for speech processing and discrimination, as it enables to keep information temporarily accessible. The verbal working memory component is maintained by the phonological loop that serves speech-related functions, such as the retrieval of words and syntax from sentences in speech, storage, manipulation, rehearsal, as well as preparation for oral language production [22, 23]. The correlations with working memory were obtained with all three investigated neural measures, indicating that both neural function and structures are linked with working memory processes that, in addition, may be related to working memory problems in dyslexia [151, 153, 194, 201, 249–251].

Overall, the associations highlight the relevance of both several brain struc-

tures and functions for reading in both typical and dyslexic readers. They further indicate the suitability of neural speech processing and neuroanatomical markers for investigating reading-related brain processes and structures, respectively.

It is important to note that correlations do not reveal causality. The finding of links between brain structure and function with reading-relevant skills cannot disentangle whether brain structure/function affect reading-relevant skills, or the other way around, or both. To truly be able to talk about causation, longitudinal training designs and clinical trials are needed in the field of neuroscientific studies of reading and its deficiencies. Another general challenge in investigating reading and reading-relevant skills is the high relations and intercorrelations of the subskills. The approach to at least partly address this challenge was to divide the extensive battery into three composite scores to reduce multiple comparison and intercorrelation problems. However, the use of different analysis models that could better take into account intercorrelations should be explored in the future.

In summary, the findings of this thesis suggest links between brain structure and function during speech processing with cognitive processes relevant for efficient reading. The associations may be explained by the constraint of early-developed oral language networks for later developing reading circuits in the brain.

5.5 Strengths, Limitations and Future Directions

This thesis reports and discusses neurophysiological and -structural findings related to dyslexia and reading-relevant skills utilizing partly novel analysis methods allowing to approach functional and structural abnormalities in dyslexia from different angles. The following aspects are specific strengths of the thesis: Both neurophysiological methods of choice (EEG and MEG) have an excellent temporal resolution, and were complemented by MRI in Studies II–IV with its accurate spatial resolution. The studied participant groups included newborns and adults. Neurophysiological studies with at-risk newborns, which are challenging and scarcely conducted, can investigate mainly genetic rather than environmental risk factors, due

to still minimal environmental influences, such as language exposure, at birth. The at-risk infants for this Study were carefully selected by applying strict criteria for parental reading and writing tests. The adult studies stand out by extensive behavioural characterization that allowed for inspecting the relationships of neural activity with reading and related skills. The choice of both controlled and natural speech stimuli (Studies I–III), as well as utilizing MEG and anatomical MRIs for spatially more accurate source localization (Studies II and III) further allowed to extend our understanding on speech-related neural deficiencies in dyslexia and how they relate to reading skills. Statistical methods used in this thesis are robust, controlling for relevant covariates and multiple comparisons. Lastly, principles of open science have been supported by preregistration and making analysis code available to work against the replication crisis. In addition to these strengths, certain limitations have to be considered.

The speech-sound *stimuli* used in Studies I and II may not have been sufficiently difficult to discriminate for dyslexic adults, as discussed earlier (Section 5.1.2). Future studies could investigate whether similar stimuli with smaller deviants, more variable contexts of stimulus presentation, or integration of sounds with written input can probe the nature of phonological deficits in dyslexia. In addition, while this thesis used both more controlled paradigms and natural speech stimuli, future research could try to combine both approaches in one paradigm, e.g., by extracting ERPs from the same continuous speech stimulus as ISCs. This could inform about the relation of ERPs and ISCs in different frequency bands during speech processing in dyslexia, and contribute to the interpretation of ISC in relation to the speech stimulus.

In addition to speech-elicited MMRs, future *infant* studies could combine several functional measures to explore their validity as individual biomarkers for dyslexia. One possibility is to extend the novel ISC method to infant and child studies to find out whether and how their natural speech processes differ from those of adults. This would pose new challenges, but also interesting opportunities to extend the use of ISC to younger populations.

The *adult* dyslexic sample used in the thesis was the same for Studies II–IV and therefore the interpretations made are strongly based on the character-

istics of this sample. It may be that the lower verbal and performance IQ in the dyslexic compared to control group could have affected the results, although these differences have been accounted for in the analysis by including the IQ as a covariate or by repeating the analysis with matched subgroups. In the future, it would be interesting to investigate different subgroups of dyslexia, such as those having problems with phonological representations vs. access, or those with specific temporal processing deficits. Understanding the specific associations between problems with reading-relevant skills and neural deficits in those possible subgroups could help to disentangle the complex phenotype of dyslexia. Another aspect for future studies would be to more closely investigate dyslexic adults that have compensated for dyslexia and their strategies to overcome possible difficulties, in order to understand protective and/or interventive methods.

VBM studies on dyslexia have used different methodological and processing criteria, as well as statistical thresholds which makes comparisons between studies more challenging. Even though the criteria used in Study IV are commonly used in the field, stricter thresholds in preprocessing and statistical testing could improve the validity of results further.

Further *integration* of neuroimaging findings with other fields, such as computer science, education, and genetics, is required for a better understanding of dyslexia from different viewpoints. Methods from computer science could improve prediction accuracy with the help of machine learning to identify high-risk individuals. If that could be accurately achieved, then education and health care providers could be involved to arrange sufficient support for these individuals. To understand the genetic basis of dyslexia better, first integration attempts between neuroimaging and genetic studies have been made [e.g., 350–352]. However, such studies are still rare and remain challenging due to very large sample sizes required for genetic analyses that are not usually obtained in the neuroimaging field.

More generally, the neuroimaging field suffers from small *sample sizes* that may not be sufficient to detect the effects of interest. This is one of the reasons for larger studies often not being able to replicate findings of previous smaller studies, resulting in the current replication crisis and a possible publication bias [see, e.g., review of 211]. Even though in this thesis mod-

erate to large sample sizes have been used, executing power analysis prior to the start of a study or combining data of different laboratories to obtain a larger sample size, could clearly lead to an improvement in the future. In practice, recruiting a large participant sample is challenged by several exclusion criteria, both related to differential diagnostics and brain imaging protocols.

6 Summary and conclusions

The results of this thesis demonstrate that dyslexia risk is reflected in deficient speech-sound processing already at birth. This neural speech processing deficit, potentially leading to inaccurate formation of phonological representations, could be a precursor of dyslexia. Neural speech discrimination could serve as a relevant biomarker to predict language and reading development, best in combination with behavioural and genetic markers, and ultimately leading to targeted support for individuals at highest risk.

Adults with dyslexia were not found to have deficiencies in neurally discriminating the same speech sounds as newborns at risk of dyslexia, possibly due to the sample not being representative of auditory processing deficits. However, during more complex stimulation, namely natural speech, adults with dyslexia had atypically synchronized neural activity. The less synchronized activity in the low delta-frequency band and more synchronized activity in higher frequency bands could reflect temporal sampling deficits of different natural speech features. Natural speech processing analyzed with appropriate methods opens new possibilities to unravel the complex neural basis of dyslexia. In addition to the functional results, structural abnormalities in dyslexia were pinpointed to areas important for reading. This might shed light on the neurogenetic origin of dyslexia and reading, or on the influence of reading exposure.

The functional and anatomical measures used in this thesis were linked to the reading-relevant skills of interest: phonological processing, technical reading, and working memory. The associations were predominantly positive, indicating that stronger or more synchronized activity during speech processing or larger neuroanatomical structures were associated with better reading-relevant performance. These links highlight the overlap of the functional speech and reading network, the structural network in the brain connected to reading, and the relevance of those neural measures in reading impairment. The links may have their origin in the overlap of oral language

networks that develop early in life and reading networks that are constrained by the language network, indicating the importance of solid oral language skills for accurate reading acquisition and performance.

Taken together, this thesis provides new insights into neural functional and structural correlates of dyslexia and its risk, contributing to uncovering the neural basis of dyslexia. The thesis findings further imply that the developed sophisticated skill of reading in humans is closely related to neural speech processing and several neuroanatomical structures.

Glossary

axons long projections of neurons that transmit the electric signals away from the neuronal cell body.

cerebellum 'little brain' in the back and bottom of the brain thought to be mainly responsible for motor and balance coordination.

corpus callosum midline brain structure that connects the left and right hemispheres of the brain.

cortex outer layer of neural tissue in the brain, characterized by specific formations of neuronal populations.

cortical oscillations rhythmic or periodic neuronal activity in the brain.

dendrites extension arms of a neuron that receive signal input from other neurons and propagate the signal to the neuronal cell body.

endophenotype a quantitative biological trait that reflects the function of a biological system and is heritable, and therefore related more to the root cause of the disease/disorder than its broad behavioural characterization.

fusiform long spindle-shaped part of the temporal and occipital lobes of the brain.

glial cells non-neuronal cells of the nervous system that provide support and insulation to neurons, e.g., by forming myelinated sheats around axons.

gyrus ridge of the folded cerebral cortex, usually surrounded by sulci.

heritability percentage of variance in a population that is due to pure genetic influences.

inferior below/bottom of a neuroanatomical structure.

myelinated myelin is a fat-rich layer surrounding the axons of neurons to insulate and allow fast and efficient transmission of electric signals in the nervous system.

neural entrainment synchronization of rhythmic activity in the brain (cortical oscillations) with the rhythm of external periodic stimuli.

neuron nerve cell, basic unit of the human nervous system.

orbitofrontal part of the frontal lobe, i.e., the prefrontal cortex, of the brain.

phoneme awareness part of phonological awareness focused on the identification and manipulation of phonemes, the smallest perceived units of sounds in speech that distinguish words.

phonological awareness perception of sound structures, i.e., that words consist of smaller units in oral language.

phonological processing analysis and manipulation of sounds in native language to process speech and print.

putamen subcortical structure in the brain that has been related to movement and learning.

sulcus depression of the folded cerebral cortex, usually surrounded by gyri.

superior above/top of a neuroanatomical structure.

supramarginal part of the parietal lobe of the brain.

synapses gap between two cells of the nervous system that transmits electric or chemical signals from the sender to the target cell.

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Clinical Neurophysiology 130 (2019) 634–646

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

An extensive pattern of atypical neural speech-sound discrimination in newborns at risk of dyslexia

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ARTICLE INFO

Article history:
Accepted 14 January 2019
Available online 12 February 2019

Keywords:
Newborn
Dyslexia
Mismatch response (MMR)
Event-related potential (ERP)
Auditory
Speech sound

HIGHLIGHTS

- Familial dyslexia risk is associated with deficient speech-sound processing already at birth.
- Mismatch responses to speech-sound changes were absent, diminished or atypical in at-risk newborns.
- Speech-processing deficits at birth might serve as early neural markers of language disorders.

ABSTRACT

Objective: Identifying early signs of developmental dyslexia, associated with deficient speech-sound processing, is paramount to establish early interventions. We aimed to find early speech-sound processing deficiencies in dyslexia, expecting diminished and atypically lateralized event-related potentials (ERP) and mismatch responses (MMR) in newborns at dyslexia risk.
Methods: ERPs were recorded to a pseudoword and its variants (vowel-duration, vowel-identity, and syllable-frequency changes) from 88 newborns at high or no familial risk. The response significance was tested, and group, laterality, and frontality effects were assessed with repeated-measures ANOVA.
Results: An early positive and right-lateralized ERP component was elicited by standard pseudowords in both groups, the response amplitude not differing between groups. Early negative MMRs were absent in the at-risk group, and MMRs to duration changes diminished compared to controls. MMRs to vowel changes had significant laterality × group interactions resulting from right-lateralized MMRs in controls.
Conclusions: The MMRs of high-risk infants were absent or diminished, and morphologically atypical, suggesting atypical neural speech-sound discrimination.
Significance: This atypical neural basis for speech discrimination may contribute to impaired language development, potentially leading to future reading problems.

1. Introduction

Difficulties in learning to read and write can lead to severe problems in social and academic development. Developmental dyslexia, affecting 4–17% of the population (Elliott and Grigorenko, 2014), is a learning impairment specific to reading and writing despite affected individuals' otherwise intact cognitive abilities. The underlying cause for dyslexia is partially genetic, i.e., the genetic variation accounts for at least 50% (DeFries and Fulker, 1985) or even up to 70–80% (Kere, 2014) of the variation in reading and related difficulties in dyslexic individuals. Several dyslexia susceptibility genes have already been identified (Kere, 2014). Dyslexia often occurs in combination with other developmental disorders, such as developmental language disorder (DLD; former: specific language impairment, SLI). Both disorders were suggested to be based on similar core mechanisms (Bishop and Snowling,

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https://doi.org/10.1016/j.clinph.2019.01.019
1388-2457/

2004), specifically phonological processing deficits and processing of time-varying acoustic events (Chandrasekaran and Kraus, 2012), and show an overlap in electrophysiological (Choudhury and Benasich, 2011), behavioral (de Wit et al., 2017), and genetic (Newbury et al., 2011) components.

Dyslexia can be diagnosed at school age, when children start to exhibit difficulties in reading-skill acquisition. If children at high risk of dyslexia could be identified and treated prior to school onset, social and academic outcomes of these children could be drastically improved (Gabrieli, 2009). A prerequisite for designing early interventions is to identify reliable markers of the deficient neural processes that may underlie dyslexia.

One of the current leading theories on dyslexia suggests that the majority of affected individuals have a phonological processing impairment, proposed to be based on a deficient formation, storage and/or retrieval of speech-sound representations in the brain (Ramus, 2001; Ramus and Szenkovits, 2008). As learning to read requires fast and accurate mapping of letters to their corresponding speech sounds in the brain, abnormal development of the speech-sound representations, or access to them, would result in inaccurate or slow assembly/access of the neural network required for fluent reading (Ramus and Szenkovits, 2008). The deficiency in the development of speech-sound representations reflected in neurophysiological responses could serve as a neural predictor for future reading problems in dyslexia (Kujala, 2007). Whereas these responses cannot yet be used in diagnostics at the individual level, this suggestion is supported by findings showing that at group level, some of these response are associated with future reading skills (for a review, see Volkmer and Schulte-Körne, 2018).

1.1. Neurophysiological means to evaluate speech-sound processing during early development

Neural speech-sound representations can be probed with the mismatch negativity (MMN; Näätänen et al., 2007), an event-related potential (ERP) component elicited at 150–250 ms after the onset of rare deviants presented among frequent standard stimuli (Näätänen, 2001). Its response amplitude is greater to large than small sound changes and correlates with behavioral change detection performance, thus reflecting stimulus discrimination accuracy (Kujala and Näätänen, 2010). The MMN has been widely used to study speech-sound processing in healthy and clinical populations (Näätänen et al., 2011). In developmental dyslexia, diminished MMN amplitudes have been found to speech- and non-speech-sound changes (Kujala and Näätänen, 2001; Kujala, 2007; Hämäläinen et al., 2013), suggesting an impairment of neural sound discrimination in dyslexia, consistent with the phonological deficit hypothesis.

Being elicited even in inattentive participants (Winkler, 2007), MMN is a feasible tool to investigate auditory processing in early infancy, even at (Alho et al., 1990) or before birth (Huotilainen et al., 2005). The infant equivalent of MMN, the mismatch response (MMR; a term also used hereafter) is often positive in polarity (Trainor, 2012) which has been suggested to arise from various factors (Kushnerenko et al., 2013). For example, positive MMRs could indicate neural immaturity and negative MMRs maturity (e.g., Mueller et al., 2012; cf. see also Leppänen et al., 2004) since, e.g., positive MMRs are most pronounced in young infants and get weaker with age (Morr et al., 2002; He et al., 2007, 2009), and negative MMRs are least pronounced in young infants and get stronger during the first year of life (Kushnerenko et al., 2002; Trainor et al., 2003; He et al., 2007, 2009). Infant MMRs of opposite polarities might reflect distinct neural processes, as they can be separated by using different filter settings (Trainor et al., 2003; He et al., 2007), differ in their scalp distribution (He et al., 2007), and can co-occur and overlap in time (Leppänen et al., 1997). Even though the exact mechanism of infant MMR generation remains unclear, regardless of response polarity, infant MMRs were suggested to be indices of auditory discrimination (Leppänen et al., 1997; Trainor et al., 2003).

Infant MMR studies have shed light on the development of early auditory abilities. For example, they have shown that already at birth, infants can discriminate duration and frequency differences (Alho et al., 1990; Leppänen et al., 1997; Čeponiene et al., 2002). They are even able to process complex sound relationships, like rules in sound patterns and musical chords (Virtala et al., 2013; Háden et al., 2015). Along with these abilities, newborns possess necessary prerequisites for language processing and, indeed, they can also neurally differentiate changes in language-relevant stimuli, such as changes in vowels, consonants, and their durations in syllables or pseudowords (Cheour-Luhtanen et al., 1995; Leppänen et al., 1999; Kushnerenko et al., 2001; Partanen et al., 2013).

1.2. Speech-sound processing in infants at familial risk of dyslexia

Familial risk of dyslexia can influence the elicitation of MMRs. Six- and two-month olds at risk of dyslexia were found to have smaller or absent MMRs than control infants at no risk of dyslexia to consonant duration changes in a pseudoword or changes in consonant-vowel-consonant (CVC) syllables, respectively (Leppänen et al., 2002; van Leeuwen et al., 2008). In newborns at risk of dyslexia, ERPs were larger than in control newborns to shorter vowels in syllables, presented as deviant stimuli among syllables with long vowels (Leppänen et al., 1999). This rather unexpected finding might result from differences in the obligatory responses (MMRs obtained from deviant-standard subtraction waves were not reported).

Importantly, longitudinal studies have shown that the presence or absence of certain auditory brain responses in early infancy is associated with future reading fluency (Van Zuijen et al., 2013; Schaadt et al., 2015). For example, later non-fluent readers were shown to have absent MMRs to consonant changes in a syllable in early infancy (Van Zuijen et al., 2013; Schaadt et al., 2015). However, no association between the absence of MMR to frequency changes in infants at risk of dyslexia and their later reading skills has been found by Leppänen et al. (2010). Possibly, neural speech-sound discrimination is more strongly associated with dyslexia than non-speech-sound processing, in line with the phonological processing deficit model. Since brain responses in infancy were found to be associated with later language development and reading skills in pre-school and school age (Molfese, 2000; Guttorm et al., 2005; Leppänen et al., 2010, 2012; Schaadt et al., 2015; Lohvansuu et al., 2018) and even earlier (Benasich et al., 2006; Cantiani et al., 2016), it is vital to determine how they deviate in those at dyslexia risk from the typical pattern. Besides group differences in MMR amplitudes, atypical hemispheric lateralization of the MMR was found in dyslexia-risk infants (Pihko et al., 1999; Guttorm et al., 2001; van Leeuwen et al., 2008; Leppänen et al., 2010). Notably, the results on lateralization of brain responses to sound and speech-sound changes, repeatedly found to be atypical in at-risk than control group, are not consistent throughout the previous studies. Some studies might be compromised by small, uneven, and/or unmatched sample sizes, and different stimuli and change types in different studies might have resulted in variable results (as, e.g., in Leppänen et al., 1999; Van Zuijen et al., 2013). Small sample sizes are particularly problematic in infant studies, as infant ERPs exhibit a large variance within and across individuals. Furthermore, as only a part of infants at familial risk of dyslexia will develop the disorder (Fisher and DeFries, 2002) and as only a subgroup of them demonstrates extensive auditory

processing deficits (Hämäläinen et al., 2013), large sample sizes are essential to detect signs of auditory dysfunctions.

1.3. Aims and hypotheses of the current study

We aimed to investigate the nature of impaired speech-sound discrimination in a large sample of newborn infants at high familial risk of dyslexia based on a parental diagnosis of moderate to severe dyslexia, using a more extensive stimulus set than previous studies. We recorded ERPs to pseudowords and MMRs to vowel duration, sound frequency of syllables, and vowel identity changes embedded in pseudowords. This is the first part of a longitudinal study (the DyslexiaBaby study, see Virtala and Partanen, 2018) in which the effects of parental dyslexia risk, and of an early passive music intervention on neural speech-sound processing and language development, will be investigated in infants from birth to pre-school or school age. The duration, frequency, and vowel deviances were chosen since the accurate detection of these features is essential in order to perceive speech sounds and word boundaries. First, we hypothesized that the ERP to the pseudoword could be diminished in at-risk infants. Second, we expected to find absent or diminished MMRs in these infants. Third, with an additional control paradigm, in which the long duration deviant was repeated alone (Schröger and Wolff, 1998), we tested whether the MMRs obtained to duration changes reflect genuine duration change detection or whether the acoustic stimulus duration differences affect the MMRs (Kushnerenko et al., 2001). Fourth, based on previous studies, both the MMRs and the ERPs to standard stimuli were expected to exhibit an atypical lateralization in high-risk infants.

2. Methods

2.1. Participants

The recruitment and participant selection process for this study is illustrated in Fig. 1. Families were recruited via traditional and social media, maternity clinics and wards, and via the website of the DyslexiaBaby study. The recruitment focused mainly on parents with dyslexia, but also control families were recruited with the same strategies. Two hundred and eight healthy full-term (gestational age at least 37 weeks, age at measurement 0.5–17 days, birth weight at least 2500 g) Finnish newborns with normal hearing, having passed the routine screening in the hospital (Evoked Oto-Acoustic Emissions, EOAE), participated in the longitudinal study.

In order to be included in the at-risk group, one or both of the infant's biological parents had to have developmental dyslexia, confirmed by a recent diagnostic statement from a health care professional or dyslexia testing in the present study, in addition to a report of reading- and writing-related difficulties in childhood. Dyslexia testing consisted of questionnaires, interviews, and a Finnish standardized test measuring oral text, word, and pseudoword reading, as well as writing speed (Nevala et al., 2006). For the at-risk group, exclusion reasons were an individualized curriculum in elementary school of the dyslexic parent (potentially indicative of broader cognitive deficits), brain trauma of the dyslexic parent in childhood (possible non-heritable cause of dyslexic symptoms of the parent), and suspected or confirmed attention deficits in one or both parents (comorbid with dyslexia and may affect auditory ERPs, see, e.g., Yang et al., 2015). The present study reports a sub-sample of high-risk infants, selected according to test results of the parents, in which for at least one parent moderate to severe dyslexia had to be confirmed by a below-norm performance of at least 2 standard deviations (*SD*) in reading or writing speed or accuracy in two or more of the subtests.

In order to be included in the control group, both of the infant's biological parents (or one on the behalf of both parents if the other parent was not available) had to report neither suspected nor diagnosed dyslexia nor other language- or learning-related disorders. Infants, whose epoched electroencephalography (EEG) data resulted in less than 50 accepted epochs for at least two deviant types were excluded (Fig. 1).

The final sample included 44 newborns at high risk of dyslexia (high-risk group), and 44 at no risk of dyslexia (control group; Table 1, Fig. 1). The groups did not differ in gender, gestational and measurement age, mothers' and fathers' educational background, or birth height and weight at a significance level of 5% (Table 1).

The Ethics Committee for Gynaecology and Obstetrics, Pediatrics and Psychiatry of the Hospital District of Helsinki and Uusimaa approved the study protocol and the study was performed in compliance with the Declaration of Helsinki. One or both parents of the newborn participants gave written informed consent to participate in the study prior to the experiment.

2.2. Stimuli and recordings

A bi-syllabic Finnish pseudoword /tata/ and its variants were used as auditory stimuli (first used by Pakarinen et al., 2014). It was uttered by a female native Finnish speaker, with the stress on the first syllable and a natural ending. The total duration of the stimulus was 300 ms, of which ≈251 ms were audible. The second syllable onset was at ≈168 ms, and the onset of the second /a/ at ≈181 ms (Fig. 2b).

In the auditory variants (Table 2), the change occurred in the second syllable, in syllable frequency (/ta-^{ta}/), vowel duration (/ta-ta:/), or vowel identity (/ta-to/). Variants were constructed by editing the /tata/ sound file (Adobe Audition CS6, 5.0, Build 708 and Praat 5.4.01). In all variants, the sound intensity level was root-mean-square (RMS) normalized to match the average intensity level of the /tata/ stimulus. Human (e.g., sigh, cry, laugh) and non-human (e.g., telephone ring, electric drill) novel sounds (duration 200 ms) were presented very rarely among the standard and deviant stimuli. Responses recorded to these stimuli will be reported elsewhere.

The sounds were presented in a mixed multi-feature-oddball paradigm (Fig. 2a) in at least four ≈7-min-long stimulus blocks. More data were recorded when the infant stayed calm. The pseudoword /tata/ was presented as the standard stimulus (probability on average 70.1%), its variants with a duration, frequency, or vowel identity change were occasionally presented as rare deviants (on average 25.3%, each individual deviant ≈8.5%), and the novel sounds were presented very rarely (on average 4.5%). One block contained 472 stimuli in total. Each deviant was presented at least 160 times and not more than 320 times during the experiment. The stimuli were presented with a varying stimulus-onset asynchrony (SOA) of 900 ± 50 ms (randomly alternating between 850, 860, 870, . . ., 940, 950 ms) in order to reduce expectancy effects related to the predictability of the stimulus onset, and to minimize an accumulation of non-phase-locked external periodic signals, such as line noise, in the ERP average. The order of the stimuli was pseudo-randomized so that two deviants and novels were never presented in a row (i.e., a deviant or novel sound was always followed by a standard). The blocks started with four standard stimuli in a row. An additional block containing a control paradigm with 200 repetitions of the vowel duration deviant only (≈3 min with the same varying SOA) was presented last, i.e., after four blocks, to obtain a controlled deviant-minus-standard difference for the duration

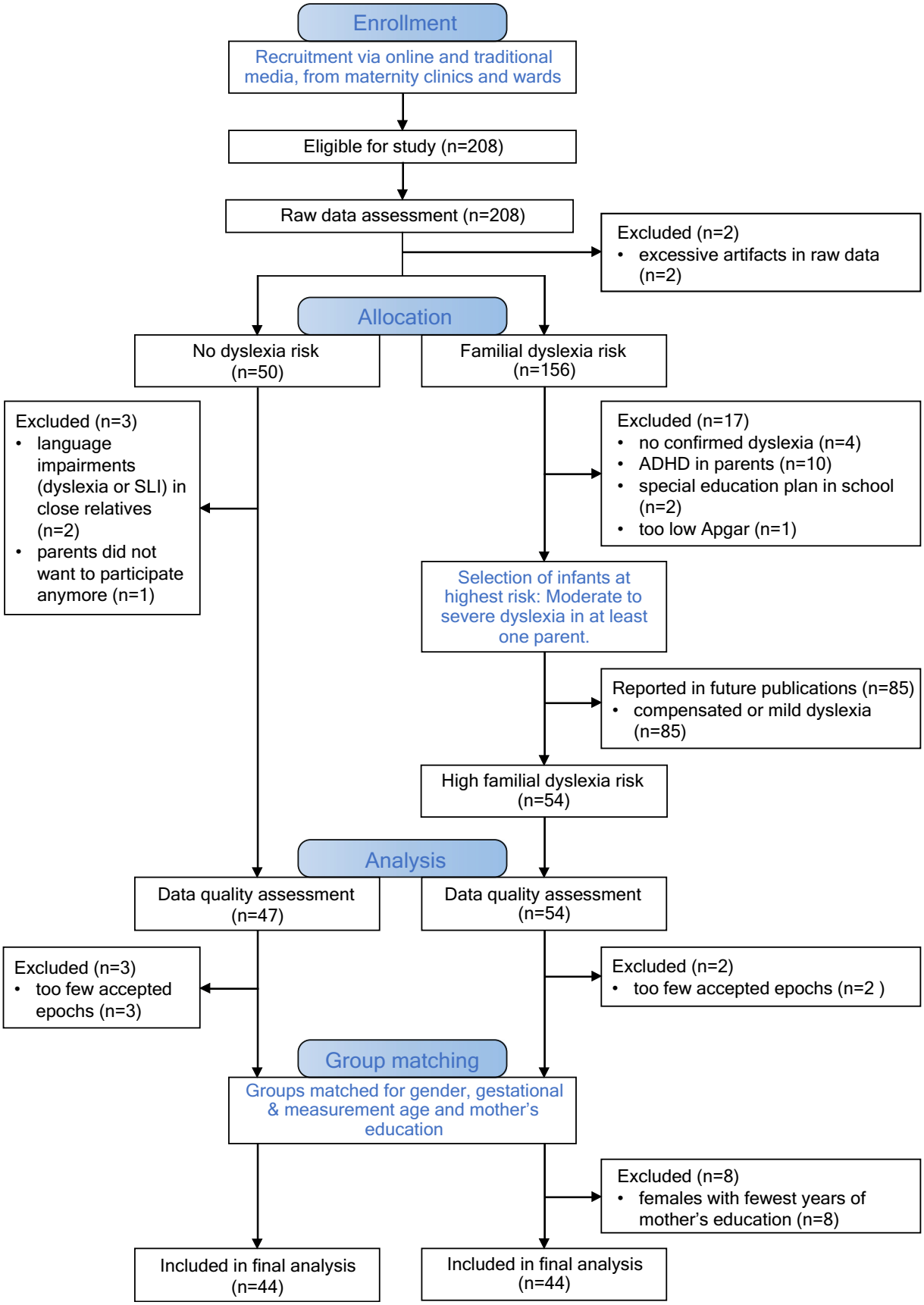

Fig. 1. Flow chart illustrating participant recruitment and allocation to groups.

Table 1
Background data (mean, *M*, in bold, and standard deviation, *SD*) of newborn participants and independent-sample *t*-statistics including degrees of freedom (*df*) and statistical significance (*p*) for group differences.

Variable	Control group		High-risk group		*T*-statistics		
	M	*SD*	***M***	*SD*	*t*	*df*	*p*
N (male/female)	44 (25/19)		44 (25/19)				
Gestational age [weeks]	**40.1**	1.1	**40.1**	0.9	0.15	86	.885
Age at measurement [days]	**8.9**	5.1	**9.1**	4.0	−0.26	86	.798
Mother's education [years]	**17.6**	2.6	**17.0**	2.2	1.06	83	.293
Father's education [years]	**16.8**	3.1	**15.5**	3.2	1.83	80	.070
Birth weight [g]	**3558**	545	**3608**	386	−0.50	86	.616
Birth height [cm]	**50.9**	2.2	**50.9**	1.9	0.05	86	.959
5-min Apgar score (range)[a]	**8–10**		**8–10**				

[a] Two high-risk infants had missing Apgar values, but were considered healthy, as there were no reported complications at birth. One high-risk infant had missing EOAE values due to a broken measurement machine, but the consequent hearing test in the maternity clinic indicated normal hearing. Therefore, these three infants were included in the final sample.

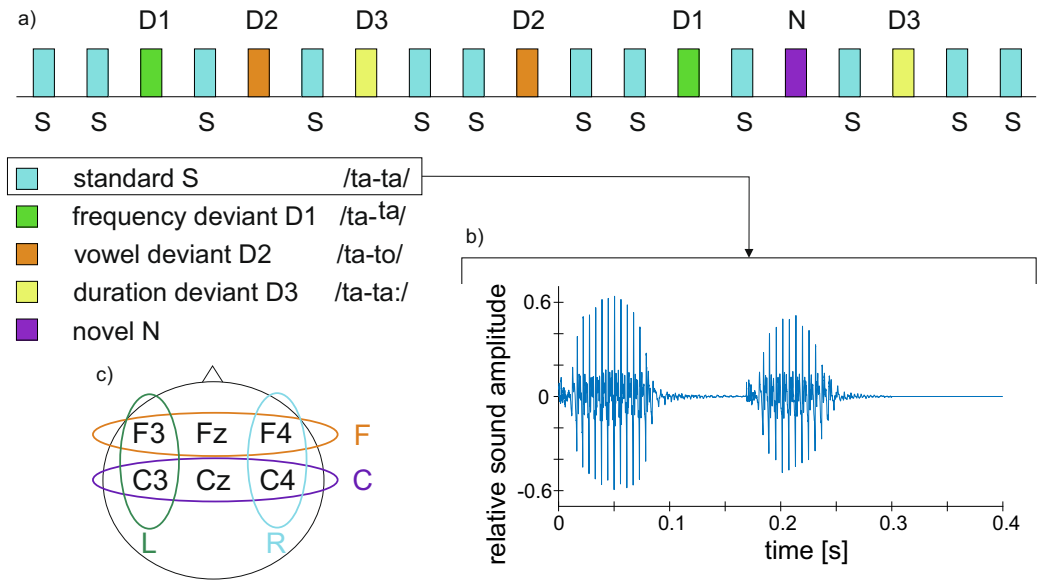

Fig. 2. Experimental setup. (a) The stimulus paradigm used. The Finnish pseudoword /tata/ was presented as a frequent standard (S, blue) and its auditory deviations (frequency, vowel and duration deviants D1–D3, green, orange, yellow, respectively) as rare deviant stimuli. Novel auditory stimuli were presented very rarely. (b) Waveform of /tata/ pseudoword. The sound amplitude is shown on a relative scale with the theoretical maximum of 1. (c) Formation of channel regions of interest (ROIs) from single EEG electrodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Description of auditory variants.

Deviant	Notation	Description of change
Duration	/ta-ta:/	Length of second syllable increased from 71 ms to 158 ms by copy and paste of the /a/-phoneme; total length 400 ms, of which approximately 327 ms were audible
Frequency	/ta-^{ta}/	Increase of fundamental frequency (F0) level of second syllable from 175 Hz to 225 Hz (5 semitones higher)
Vowel change	/ta-to/	Replacement of second /ta/ syllable with /to/ syllable as part of naturally uttered pseudoword /ta-to/ (Pakarinen et al., 2014); start time and duration of second syllable matched to /tata/ stimulus; F0-controlled to match F0-level of /tata/ stimulus

deviant. The total experiment duration was approximately one hour.

EEG recordings (sampling rate: 500 Hz, low-pass filter: 100 Hz, high-pass filter: 0 Hz) were carried out at Jorvi Hospital of Helsinki University Hospital in Espoo, and at a laboratory of the University of Jyväskylä, both in Finland. EEG was recorded with 18 active electrodes (headcap: ActiCap; amplifier: BrainProducts QuickAmp 10.08.14; software: BrainVision Recorder 1.20.0801; all: Brain Products GmbH, Gilching, Germany) placed according to the international 10/20 system (Fp1/2, F7/8, F3/4, Fz, C3/4, Cz, P7/8, P3/4, Pz, Oz, LM, RM). The data were referenced online to the average of all electrodes.

During the recording, the newborns were lying on their back in a crib and the auditory stimuli were presented with Presentation 17.2 Software (Neurobehavioural Systems Ltd., Berkeley, CA, USA) via a Genelec speaker placed approximately 40 cm from the newborn's head. The stimulus intensity was ≈65 dB at the infant's head (sound pressure level, SPL), the background noise of the room being ≈40 dB (SPL). The recording was conducted by a trained nurse or research assistant in a quiet hospital room (at Jorvi Hospi-

tal) or sound-proof laboratory (at University of Jyväskylä) who also determined the state of the infant with button presses on a response box (Cedrus RB844, Cedrus Corporation, California, USA) as 'active sleep', 'quiet sleep', 'awake', or 'intermediate sleep stage'. This classification was based on the guidelines of Grigg-Damberger (Grigg-Damberger et al., 2007). Infants of both groups spent equal relative amounts of time in active sleep (41% in control, 40% in high-risk group), quiet sleep (16% in control, 21% in high-risk group) and awake (19% in control, 15% in high-risk group) states.

2.3. Data analysis

The EEG data were pre-processed with MATLAB Release 2015a and 2017a (The MathWorks, Inc., Natick, Massachusetts, USA) as well as MATLAB toolboxes EEGlab 13.5.4b (Delorme and Makeig, 2004) and CBRUPlugin2.0b (Tommi Makkonen, Cognitive Brain Research Unit, University of Helsinki). First, data were inspected visually, and channels with continuous noise (e.g., due to poor scalp contact) were excluded from further analysis. Then, the data were filtered offline using a Hamming-windowed sinc finite impulse response filter between 0.5 (high-pass, 0.25 Hz cutoff frequency) and 25 Hz (low-pass, 28.125 Hz cutoff frequency). Thereafter, stimulus blocks with visually identified excessive movement artifacts were excluded from the analysis, and data of other blocks, except for the duration control block, were combined. Finally, the data were segmented into −100 to 840 ms epochs around stimulus onset separately for each stimulus, channel, and participant. The epochs of those standard stimuli that were immediately following a deviant were excluded from the analysis. Baseline correction was applied −100 to 0 ms prior to stimulus onset. The epochs with an amplitude exceeding ±120 μV in electrodes close to the eyes (Fp1, Fp2) were excluded to reduce eye-movement related artefacts. For all electrodes, epochs with amplitudes exceeding ±3 *SD* from the mean of the individual participant's average for each stimulus type and epochs with a drift of more than 80 μV from the start to the end of the epoch were rejected. The mean number of accepted epochs did not differ between groups (Table 3). As the final step of pre-processing, the data were re-referenced to the average of four electrodes: both mastoids (LM, RM) and electrode locations close to the mastoids (P7, P8) in order to display largest response amplitudes on fronto-central electrodes and to reduce the effects of often poor data quality on the mastoid electrodes. In 22 recordings, mastoids (20 cases, 8 in control, 12 in high-risk group) or P7/P8 (2 cases, 1 in control, 1 in high-risk group) had a poor signal, so that only mastoids or only P7 and P8 were used as references.

Six fronto-central electrodes were divided into four channel regions of interest (ROI): frontal, central, left, and right (Fig. 2c). In each ROI, the epoched data from the channels were averaged together in order to improve the signal-to-noise ratio, separately for each infant and stimulus type. Difference waves were obtained for all participants and each deviant by subtracting the standard-stimulus waveform from the deviant-stimulus waveform. Baselines were re-applied to −100 to 0 ms prior to change onset instead of stimulus onset and therefore differed between the deviants: for duration deviant 125–225 ms (change onset at 225 ms), and for frequency and vowel identity deviants 80–180 ms (change onset at 180 ms). For the duration change, an additional 'controlled' duration difference wave was calculated by subtracting the ERP elicited in the duration control block from the duration change waveform obtained in other recording blocks.

Amplitudes of ERP components to the standard stimulus and MMR amplitudes to the three deviant types were analyzed. The latencies of interest were determined by visual inspection of grand average ERPs to standard stimuli and deviant-minus-standard subtraction waveforms to each deviant type. Maximal peaks of grand average ERPs for standard stimuli and difference waves for deviant types were identified and a 100-ms (for broad reponses) or 50-ms (for narrow responses) time window (TW) was chosen centered at this peak latency. For ERPs/MMRs with several peaks, the corresponding amount of TWs was selected, so that they covered ERPs/MMRs of both groups. This resulted in two TWs (TW 1, TW 2) to the standard stimulus, in three TWs (TW I, TW II, TW III) to duration and frequency changes, and in four TWs (TW I, TW II, TW III, TW IV) to vowel identity changes. The MMR to the duration control stimulus was calculated from one TW (TW III). TW I (referred to as early MMR responses from now on) represents activity that has its peak between 200 and 500 ms from stimulus onset. TW II represents activity that has its peak between 500 and 700 ms, TW III between 700 and 800 ms, and TW IV later than 800 ms, all from stimulus onset (referred to as late MMR responses from now on).

To test whether the ERPs and MMRs were statistically significant at an alpha level of 0.05, the mean ERP/MMR amplitudes in the chosen TWs were compared to zero using one-sample *t*-tests at the ROI with the maximal response amplitude (one test per TW at the maximum ROI, equals 13 one-sample *t*-tests). Effect sizes are reported as Cohen's *d*. The statistical analyses were carried out with SPSS 24 (IBM, Armonk, New York, US).

Repeated-measures ANOVAs (2 × 2) were separately run for the responses elicited by the standard stimulus and each deviant type (duration, duration control, frequency, vowel identity) and each TW (1, 2, I, II, III, IV) with frontality (F, C) as within-subjects factor and group (control, high-risk) as between-subjects factor (one ANOVA per TW, equals 12 ANOVAs, as TW1 of ERPs to standard responses was not significant in any group). Amplitude differences between the groups were assessed only if the ERP/MMR amplitude differed statistically significantly from zero (hereafter: was significant) in at least one group.

Front-back distributions and their interactions with group were assessed only if the ERP/MMR was significant in both groups using similar ANOVAs as above (one ANOVA per TW for responses significant in both groups, equals 5 ANOVAs). Hemispheric differences and laterality × group interactions were investigated applying the same criteria with separate ANOVAs with laterality (L, R) as within-subjects and group (control, high-risk) as between-subjects factor (one ANOVA per TW for responses significant in both groups, equals 5 ANOVAs).

Table 3
Means (*M*, in bold) and standard deviations (*SD*) of accepted epochs for standard and deviant stimuli in control and high-risk groups and independent-samples *t*-statistics including degrees of freedom (*df*) and significance levels (*p*) for differences of accepted epochs between groups.

Deviant	Control group		High-risk group		*T*-statistics		
	M	*SD*	***M***	*SD*	*t*	*df*	*p*
Standard	**487**	153	**529**	140	−1.32	86	.188
Duration	**102**	33	**110**	30	−1.20	86	.232
Frequency	**103**	32	**111**	31	−1.15	86	.253
Vowel identity	**104**	34	**112**	30	−1.08	86	.282
Duration control	**131**	27	**136**	27	−0.80	84	.426

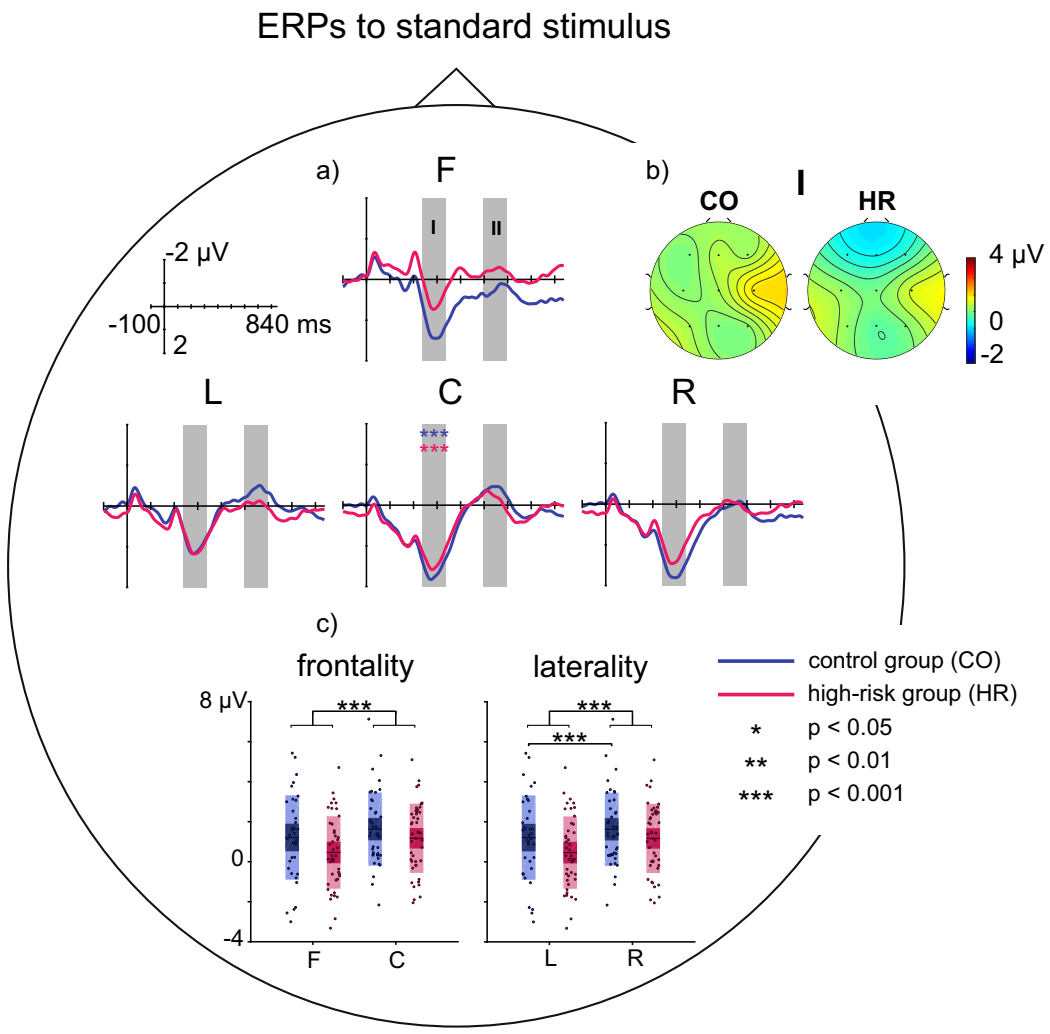

Fig. 3. ERPs to standard stimulus /tata/ from the control group (CO, blue) and high-risk group (HR, pink). (a) Grand average ERPs in control and high-risk group at channel regions of interest F (frontal), C (central), L (left), and R (right). Colored asterisks indicate the level of significance of the standard response in the selected time window for the ROI with maximal amplitude for the respective group as verified by one-sample t-tests. (b) Distribution of standard ERPs on the scalp for the early positivity (I). (c) Frontality, laterality and group effects. Each individual data point reflects the average mean amplitude of one participant, dark horizontal bars are group means, dark shaded areas mark standard errors of group means, and light shaded areas mark standard deviations. Asterisks indicate the level of significance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
ERP amplitudes of both groups (control group, high-risk group) to the standard stimulus. listed are means (in bold) in µV and standard deviations (in parentheses) in µV at the channel region of interest (C – central channels) with the maximal amplitude in selected time windows (TW; 1, 2), and one-sample *t*-statistics (*t*, *df* – degrees of freedom, in parentheses, *p* – significance level, Cohen's *d* – effect size). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

ERP	Control group	High-risk group
TW 1 (233–333 ms)	*****1.62** (1.83) on C $t(40) = 5.70$, $p < .000$, $d = 0.89$	*****1.17** (1.73) on C $t(43) = 4.49$, $p < .000$, $d = 0.68$
TW 2 (497–597 ms)	−**0.39** (1.57) on C $t(40) = -1.60$, $p = .117$, $d = -0.25$	−**0.40** (1.46) on C $t(43) = -1.81$, $p = .077$, $d = -0.27$

Applicable corrections (Huynh-Feldt) were used when sphericity was violated (original degrees of freedom and corrected *F*- and *p*-values are reported). In post-hoc comparisons, Bonferroni correction was applied, and only corrected *p*-values are reported. Effect sizes are reported as partial eta squared (η_p^2).

3. Results

3.1. ERPs to standard /tata/

The pseudoword /tata/ evoked similar ERPs in both groups (Fig. 3a, scalp distribution in Fig. 3b). Visual inspection of the waveform suggested that the pseudoword elicited two narrow early negative deflections that are most likely onset responses to the two syllables of the pseudoword, followed by a broad positivity-negativity complex (Fig. 3a). The early positive component (233–333 ms, TW 1) was statistically significant (hereafter: significant) in both groups (Table 4) and did not significantly differ between groups in amplitude ($p = .128$). ANOVA results (Table 5, Fig. 3c) revealed that the response was significantly larger at central compared to frontal channels (TW 1, frontality main effect, $p < .001$), and significantly larger at the right than left hemisphere (TW 1, laterality main effect, $p < .001$). A significant laterality × group interaction effect was found ($p = .008$), and post-hoc

Table 5
Results of the repeated-measures ANOVAs. Shown are *F*-values with degrees of freedom (*df*1, *df*2), statistical significance (*p*) and effect sizes (η_p^2) of significant and trending group (control, CO vs. high-risk, HR), frontality (frontal vs. central), laterality (left vs. right), and interaction effects for all ERP components to the standard stimulus (STD) and MMRs to speech-sound deviants (DUR - duration, DURC - controlled duration, FRE - frequency, VOW - vowel, in all time windows, TW, polarity, pol., indicated as positive, +, or negative, −) and their significant or trending post-hoc comparisons (mean difference, *MD*, and standard error of mean, *SEM*, and statistical significance, *p*). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

Component	ANOVA				Post-hoc comparisons			
TW (pol.)	Effect	*F(df1, df2)*	*p*	η_p^2	Comparison	*MD (SEM)* [μV]	*p*	Result
ERPs to STD								
1 (+)	Group	2.37(1, 74)	.128	.03				
	Frontality	23.79(1, 74)	***<.001	.24	Frontal vs. central	−0.699 (0.143)	***<.001	Frontal < central
	Laterality	19.19(1, 65)	***<.001	.23	Left vs. right	−0.505 (0.115)	***<.001	Left < right
	Laterality × group	7.56(1, 65)	**.008	.10	Left vs. right in CO	−0.823 (0.171)	***<.001	Left < right in CO
2 (−)	ERP not significant in any group, no further statistical analysis							
MMRs to DUR								
I (−)	Group	4.54(1, 74)	*.036	.06	HR vs. CO	0.750 (0.352)	*.036	HR < CO
II (+)	Frontality	4.68(1, 74)	*.034	.06	Frontal vs. central	0.598 (0.276)	*.034	Frontal > central
III (+)	Laterality × group	3.89(1, 65)	.053	.06				
MMRs to DURC								
III (+)	No significant group, frontality, laterality, and interaction effects							
MMRs to FRE								
I (−)	Group	3.36(1, 74)	.071	.04				
II (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
III (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
MMRs to VOW								
I (+)	No significant group effect; frontality, laterality effects, and their interaction with group not tested							
II (+)	Group	3.18(1, 74)	.079	.04				
III (+)	Laterality × group	4.41(1, 65)	*.040	.06	HR vs. CO at right	−1.283 (0.662)	.057	
					Left vs. right in CO	−0.860 (0.358)	*.019	Left < right in CO
IV (+)	No significant group, frontality, laterality, and interaction effects							

tests indicated that the response was significantly larger at the right than left hemisphere in the control group only ($p < .001$). The late negative response (497–597 ms, TW 2) was not significant in either group (Table 4, cf. at central channels in high-risk group, $p = .077$), and thus, no further statistical analysis was pursued.

3.2. MMRs to duration, frequency, and vowel identity changes

MMRs to speech-sound changes in duration, frequency, and vowel identity are illustrated in Fig. 4a, MMRs to controlled duration changes in Fig. 5, and the results on tests comparing them to zero are listed in Table 6. Duration changes elicited a significant negative MMR in the control group at 290–340 ms after stimulus onset (TW I), but no such response in the high-risk group. In addition, these changes elicited a significant positive MMR at 502–602 ms (TW II) and 677–777 ms (TW III) in both groups. Duration changes in the controlled duration condition elicited a significant positive MMR at 641–741 ms (TW III) in both groups. Frequency changes elicited no significant negative MMR in the high-risk group, but in the control group a significant negative response was found at 252–302 ms (TW I). A significant positive MMR to frequency changes was elicited at 578–678 ms (TW II) and 740–840 ms (TW III) in the high-risk group only. Vowel changes elicited a broad positive MMR, which was significant in the high-risk group at 715–765 ms (TW III) and 790–840 ms (TW IV), and in the control group at TWs I–IV.

The ANOVA results on MMR group, frontality, laterality, and their interaction effects are visualized in Fig. 4c and summarized in Table 5. To duration changes, the negative MMR (TW I) was significantly smaller in high-risk than in control infants (group main effect, $p = .036$). The positive MMR to duration changes (TW II) was significantly larger at frontal than central channels across groups (TW II, frontality main effect, $p = .034$). For TW III, a laterality × group interaction did not reach significance ($p = .053$). In the controlled duration change condition, no significant group, frontality, laterality, or interaction effects were found. Although in Fig. 4 there seem to be amplitude differences to frequency (TW I) and vowel changes (TW II), results did not reach significance ($p = .071$ and .079, respectively). To vowel identity changes at TW III, a significant laterality × group interaction was found ($p = .040$), driven by significantly smaller MMRs in the left compared to right hemisphere in the control group only ($p = .019$).

4. Discussion

This study aimed at determining the nature of deficits in neural encoding and discrimination of speech sounds in newborn infants at familial risk of dyslexia. To this end, ERPs to a repeated Finnish pseudoword /tata/ and MMRs to three types of changes embedded in it were recorded from newborns at high familial risk or no familial risk of dyslexia, and the response amplitudes and scalp distributions were compared between the groups. An early positive ERP component to the pseudoword was elicited at 233–333 ms in both groups, the response amplitudes not differing between the groups. However, the MMRs to speech-sound changes differed between the groups in several ways: Firstly, at early latencies negative MMRs to duration (at 290–340 ms) and frequency changes (at 252–302 ms) were elicited in the control group, but were absent in the high-risk group. A group comparison at these early latencies indicated significantly smaller MMR amplitudes to duration changes. Secondly, the high-risk group had late positive MMRs (at 578–678 ms and 740–840 ms) to frequency changes, which were absent in the control group. Thirdly, late positive MMRs (at 715–765 ms) were lateralized to the right hemisphere for vowel changes in the control group. Taken together, these results suggest an extensive pattern of speech discrimination dysfunctions in newborns with a high familial risk of dyslexia.

4.1. ERPs to standard pseudowords

The repeating pseudoword elicited an early positive ERP response with a central- and right-preponderant scalp distribution in both groups. The standard ERP waveform consisted of two main

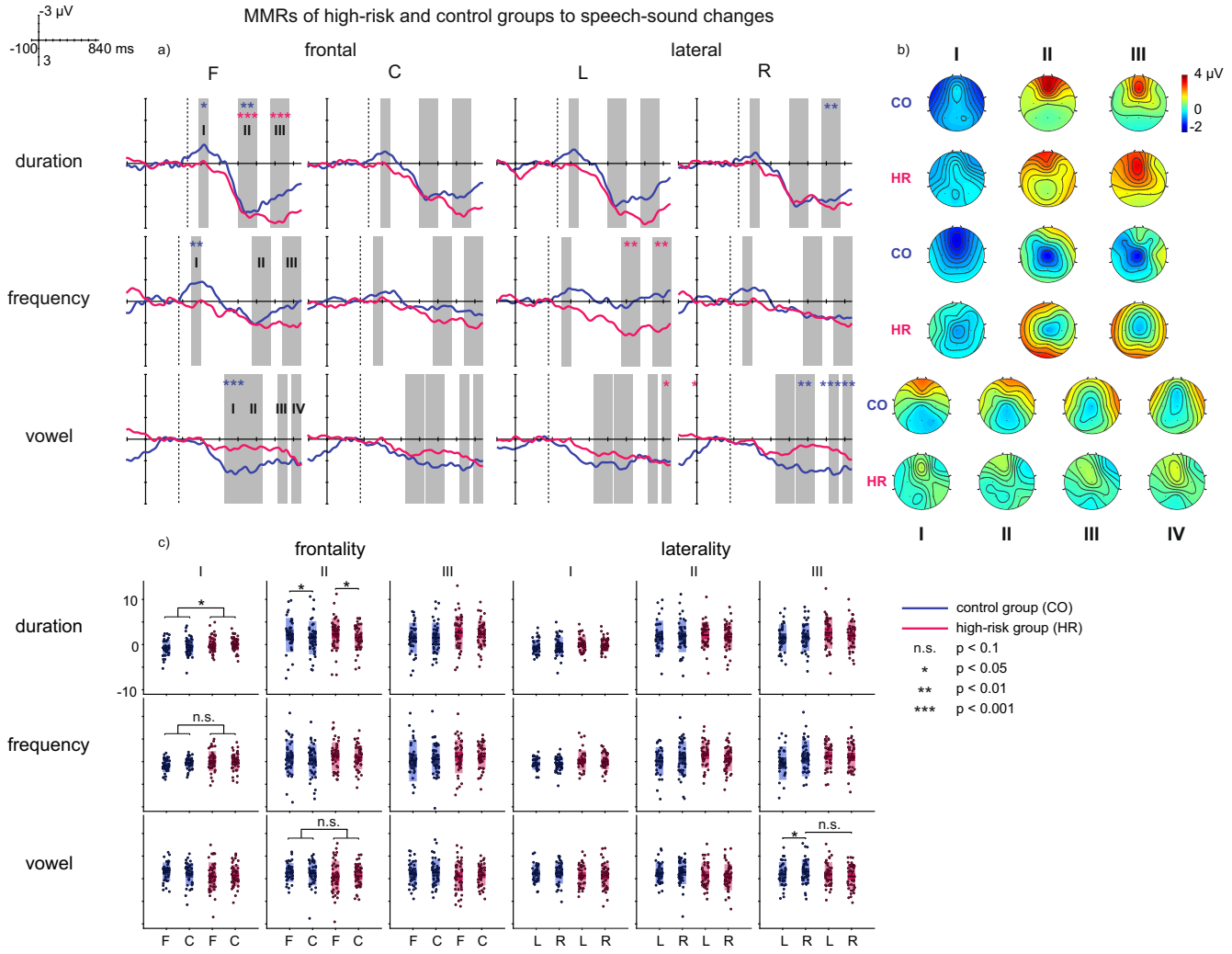

Fig. 4. MMRs at channel regions of interest F (frontal), C (central), L (left), and R (right) of the high-risk (pink) and control groups (blue) to duration, frequency, and vowel identity changes. (a) Difference curves. Change onset is marked by a vertical dotted bar preceded by a pre-stimulus baseline of 100 ms. Latency windows are marked with a gray bar and roman numerals (referred to in the text). Asterisks depict MMRs' significances on the ROI with maximal amplitude as evaluated by one-sample *t*-tests. Groups are differentiated by colours. (b) Distribution of MMRs on the scalp in the control group (CO) and high-risk (HR) group in all latency windows marked by roman numerals. (c) Frontality, laterality, and group effects. Each individual data point represents the mean MMR amplitude of one participant, dark horizontal bars are group means, dark shaded areas mark standard errors of group means, and light shaded areas mark standard deviations. Asterisks and n.s. indicate the level of statistical significance for group, hemispheric, or post-hoc comparisons of interaction effects (depicted by horizontal bars) resulting from ANOVA analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

components: an early positivity peaking at 283 ms and a wide late negativity peaking at 547 ms from stimulus onset, consistent with previous studies (Molfese, 2000; Guttorm et al., 2001; Wunderlich et al., 2006). While the early positivity was significant in both groups with relatively large effect sizes, the negative response was not significant in either group. No group differences were found for the amplitudes or hemispheric distribution of the early positivity, which suggests that familial risk of dyslexia might not influence this early level of basic speech-sound encoding.

The distribution of the early positive ERP component in the present study was maximal over the right hemisphere at central channels in both groups. Hemispheric lateralization of speech processing in infants has varied between studies, with some suggesting an enhanced left-hemispheric lateralization (Molfese et al., 1975; Dehaene-Lambertz, 2000), and others suggesting right-hemispheric processing (Perani et al., 2011). Also ERPs to tones with different harmonics were found to be larger over the left than right hemisphere (Dehaene-Lambertz, 2000), suggesting left-lateralized processing for non-speech sounds in infants. Our results with a right-hemispheric lateralization of the responses to the standard stimuli are in line with the functional magnetic resonance imaging (fMRI) study by Perani et al. (2011) in newborns. In our study, the large number of subjects (88 newborns) and the number of analyzed EEG epochs for standard stimuli were large rendering a good signal-to-noise ratio (mean of 508 artifact-free EEG epochs). Therefore, the results can be considered reliable. However, they should be confirmed with a method yielding better source-localization accuracy. To summarize, the ERPs to pseudowords suggest that the cortical encoding of repetitive speech sounds might not be influenced by familial dyslexia risk at birth and, further, that speech processing or auditory processing in general might be differently lateralized at birth than later in development.

4.2. Group differences in MMR amplitudes

In contrast with the non-existent group differences for the ERPs to the standard stimulus, the MMRs to speech-sound deviants differed between the groups in several ways. We found early negative MMRs to duration and frequency changes in control infants that

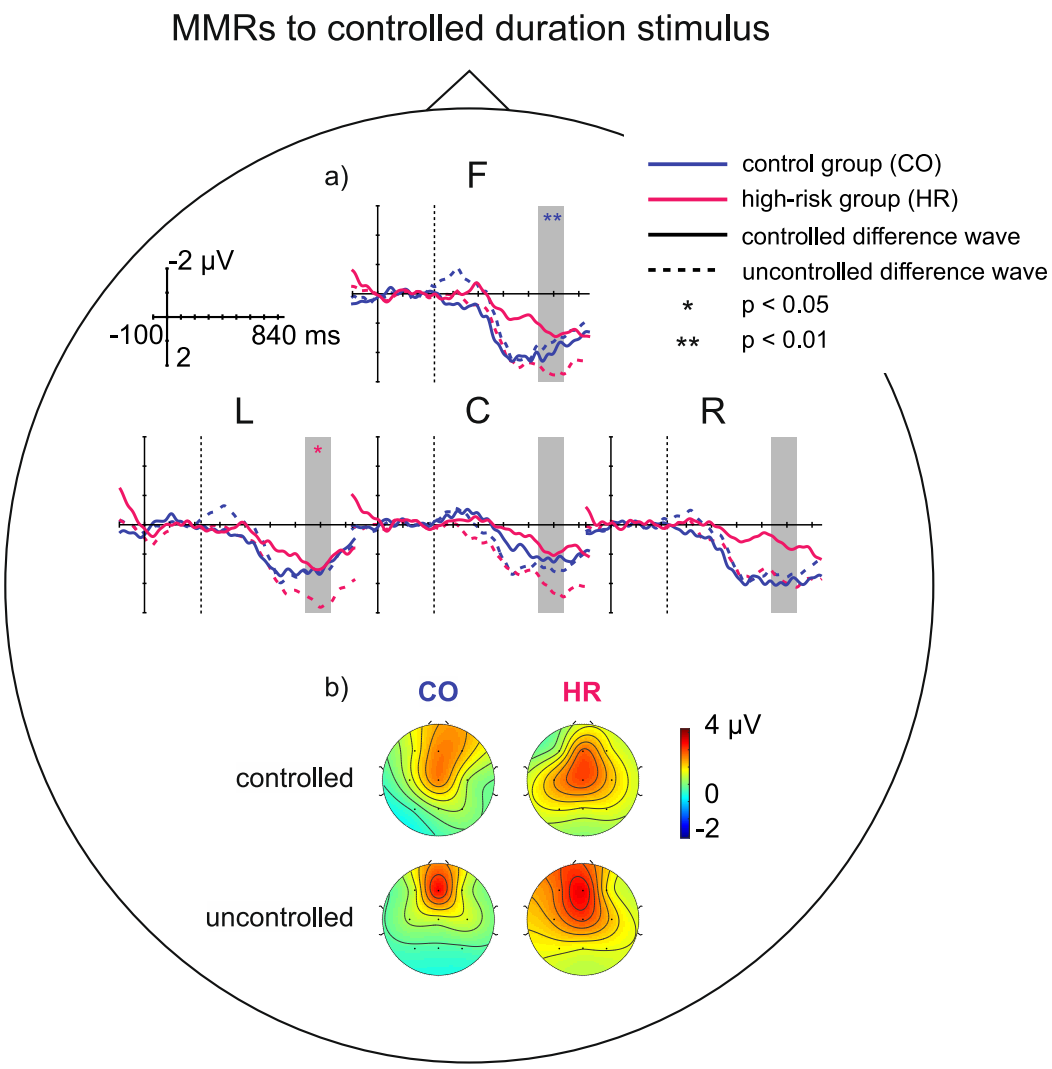

Fig. 5. (a) MMRs (difference waves) in the controlled duration condition (continuous line; duration deviant ERP was compared to the ERP to the same stimulus acting as a standard) compared to uncontrolled condition (dotted line). Change onset is marked by a vertical dotted bar preceded by a pre-stimulus baseline of 100 ms and the latency of interest is marked with a gray bar. Asterisks depict the controlled MMRs' significances as evaluated by one-sample *t*-tests. Groups are differentiated by colours. (b) Distribution of MMRs in controlled (641–741 ms) and uncontrolled (677–777 ms) conditions on the scalp for control group (CO) and high-risk (HR) group.

were absent in high-risk infants. Furthermore, the comparison of the early MMR amplitudes between the groups indicated significantly smaller amplitudes to duration changes in the high-risk than control group. Late positive MMRs to frequency changes were only present in the high-risk group and absent in the control group. Vowel changes, in turn, elicited late positive MMRs in both groups. Previous studies demonstrating deficient auditory processing in newborns at risk of language impairments used non-speech sounds (Leppänen et al., 2010), speech sounds with one deviant type only (consonant duration, Leppänen et al., 1999), or involved older infants (Leppänen et al., 2002; Benasich et al., 2006; van Leeuwen et al., 2008; Van Zuijen et al., 2013; Schaadt et al., 2015). In our study, absent or diminished MMRs were found to two out of three deviant types presented to infants at high risk of dyslexia, suggesting several neural change detection irregularities in high-risk infants already at birth.

In the present study, MMRs of both negative and positive polarity were elicited in newborns, consistent with some previous studies (Friederici et al., 2002; Háden et al., 2009; Virtala et al., 2013). Whereas duration, frequency, and vowel deviants demonstrated a positive MMR around 250–600 ms from stimulus onset in both groups (except for frequency change in the control group), it was preceded by a negative deflection at around 250–350 ms in response to the duration and frequency changes in the control group only. Co-existing negative and positive MMRs have been reported also previously in infants, as reviewed in the introduction. In the present study, the negative responses to the duration and frequency deviants peaked very early, at around 90 ms and 100 ms from deviance onset, respectively. Similar early-latency negative responses to auditory deviants have been reported in infants also previously (Kushnerenko et al., 2007; Háden et al., 2009).

The emergence of an early negative component in the difference waveform has been interpreted as a sign of neural maturation (Trainor et al., 2003). The co-existence of fast negative MMRs and slow positive MMRs in the present results could thereby reflect a maturational stage where the negative MMR starts to appear, while the positive MMR gradually disappears. Alternatively, the positive MMR was suggested to develop towards the adult P3a, reflecting maturation of the auditory attention network (Kushnerenko et al., 2013). While the maturational pathways of the negative and positive MMRs and their underlying functions are still under debate, both components are thought to reflect aspects of an auditory change detection mechanism in infancy,

Table 6
MMR amplitudes of both groups (control group, high-risk group) to the deviant types (DUR – duration, DURC – controlled duration, FRE – frequency, VOW – vowel). Listed are means (in bold) in μV and standard deviations (in parentheses) in μV at the channel region of interest (F – frontal, C – central, R – right, L – left channels) with the maximal amplitude in selected time windows (TW; I, II, III, IV), and one-sample *t*-statistics (*t*, *df* – degrees of freedom, in parentheses, *p* – significance level, Cohen's *d* – effect size). Statistical significance is marked with asterisks ($^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$).

MMR	Control group	High-risk group
DUR TW I (290–340 ms)	*−**0.75** (1.82) on F $t(35) = -2.48$, $p = .018$, $d = -0.41$	−**0.06** (1.44) on R $t(42) = -0.28$, $p = .783$, $d = 0.04$
DUR TW II (502–602 ms)	****2.12** (3.77) on F $t(35) = 3.38$, $p = .002$, $d = 0.56$	*****2.34** (3.47) on F $t(42) = 4.42$, $p < .000$, $d = 0.67$
DUR TW III (677–777 ms)	****1.69** (3.08) on R $t(40) = 3.52$, $p = .001$, $d = 0.55$	*****2.65** (3.72) on F $t(42) = 4.68$, $p < .000$, $d = 0.71$
DURC TW III (641–741 ms)	****1.99** (3.64) on F $t(33) = 3.19$, $p = .003$, $d = 0.55$	***1.41** (3.38) on L $t(37) = 2.58$, $p = .014$, $d = 0.42$
FRE TW I (252–302 ms)	**−**0.85** (1.48) on F $t(35) = -3.45$, $p = .001$, $d = -0.57$	−**0.04** (1.88) on C $t(43) = -0.16$, $p = .877$, $d = -0.02$
FRE TW II (578–678 ms)	**0.86** (3.98) on F $t(35) = 1.30$, $p = .202$, $d = 0.22$	****1.47** (2.87) on L $t(37) = 3.17$, $p = .003$, $d = 0.51$
FRE TW III (740–840 ms)	**0.74** (3.99) on R $t(40) = 1.19$, $p = .241$, $d = 0.19$	****1.27** (2.79) on L $t(37) = 2.80$, $p = .008$, $d = 0.45$
VOW TW I (422–522 ms)	*****1.50** (2.09) on F $t(35) = 4.29$, $p < .000$, $d = 0.71$	**0.70** (2.37) on C $t(43) = 1.96$, $p = .057$, $d = 0.30$
VOW TW II (536–636 ms)	****1.43** (2.65) on R $t(40) = 3.44$, $p = .001$, $d = 0.54$	**0.79** (2.80) on L $t(37) = 1.75$, $p = .088$, $d = 0.28$
VOW TW III (715–765 ms)	*****1.56** (2.72) on R $t(40) = 3.68$, $p = .001$, $d = 0.57$	***0.96** (2.72) on L $t(37) = 2.18$, $p = .035$, $d = 0.35$
VOW TW IV (790–840 ms)	****1.32** (2.87) on R $t(40) = 2.94$, $p = .005$, $d = 0.46$	***1.14** (2.97) on L $t(37) = 2.37$, $p = .023$, $d = 0.38$

essential for and likely indicative of future sensory-cognitive development. The present results demonstrated negative MMRs in the control group only, whereas MMRs in high-risk infants had a positive polarity. In light of the above-reviewed literature, the missing negative MMRs in the high-risk group and the missing positive MMR in the control group to the frequency change could be interpreted as signs of less mature auditory neural development in the high-risk infants. As the negative MMR had an earlier latency than the positive MMR, neural auditory change detection in the control group can also be interpreted to be faster than in the high-risk group.

The absent early MMRs in the high-risk group to duration and frequency changes, and MMR amplitude differences between groups to duration changes suggest that the auditory system of the control group can distinguish more accurately between the different speech-sound changes than that of the high-risk group, in line with previous results showing diminished MMNs in dyslexic adults (Baldeweg et al., 1999; Kujala et al., 2003) and children (Maurer et al., 2003; Lovio et al., 2010). Also in young infants, similar evidence converges, as reviewed in the introduction.

The results of the aforementioned infant studies and our study demonstrate atypical speech-sound discrimination due to familial risk of dyslexia already in infancy. The ability to extract accurately speech-sound information and to discriminate speech sounds is important for typical language development involving the formation of neural representations of native language phonemes during the first year of life (Kuhl, 2004). Consequently, atypical speech-sound discrimination at birth could lead to a weak or slow formation of native language phoneme representations. This is supported by studies showing that poorer neural speech processing in infancy as demonstrated by auditory ERPs predicts compromised language skills in childhood (Molfese, 2000; Guttorm et al., 2005; Leppänen et al., 2010, 2012; Schaadt et al., 2015; Lohvansuu et al., 2018). Furthermore, the discrimination of, e.g., duration and frequency cues investigated in the present study is important for the detection of word boundaries (Friederici, 2005). They have to be detected to differentiate between single phonemes and to segment words during the filtering process of the incoming continuous speech stream (Jusczyk, 1999), which is relevant for language development. Problems in detecting word boundaries can therefore lead to further challenges in later language development. Several factors can influence the course of this future language development. With newborns, as examined in this study, it is possible to observe how speech stimuli are originally processed, prior to extensive influence from experience or environmental exposure. Each infant will then undergo maturational processes that depend largely both on genetic and environmental factors, which differ for each individual.

4.3. Effects of the controlled duration paradigm

The controlled duration paradigm was introduced to test whether the MMRs obtained reflect genuine duration discrimination instead of processing of the physical stimulus duration differences (Schröger and Wolff, 1998). As our duration deviant lasted 100 ms longer than the /tata/ standard, these physical differences in the offsets of the standard and deviant stimuli could result in a deflection in the difference waveform that reflected processing of merely physical differences between the stimuli. The early negative MMR that was observed in the uncontrolled duration condition in infants at no risk was not seen in the controlled condition. It may be that this early negativity was elicited due to the physical features of the stimulus change, i.e., longer stimulus duration resulting in a different obligatory ERP response (Jacobsen and Schröger, 2003). However, we found that a late positive MMR was still elicited in both groups when the stimulus differences were controlled for (i.e., when the duration deviant ERP was compared to the ERP to the same stimulus acting as a standard in the control condition). This supports and extends previous findings that the infant MMR reflects genuine change detection in the auditory system (Kushnerenko et al., 2002; Háden et al., 2016). Future studies should further investigate, what kind of sensory and cognitive functions these early negative and late positive MMRs reflect at birth.

4.4. MMR scalp distributions

We found significant interactions between laterality and group to vowel changes in the late positive MMR, which resulted from right-lateralized processing in the control group, whereas no such

effect was found in the high-risk group. This laterality finding of the present study is rather unexpected, since processing of speech in adults has repeatedly been suggested to be left-lateralized (Kimura, 1967; Tervaniemi and Hugdahl, 2003). Furthermore, in newborns and 2-month-old infants, left-lateralized MMRs were previously found in a healthy control group and right-lateralized MMRs in a group at risk of dyslexia to syllable duration changes (Pihko et al., 1999) and CVC syllable changes (van Leeuwen et al., 2008). Yet, some earlier findings on the lateralization of auditory change discrimination are consistent with ours. For example, control newborns and 2-month-old infants that turned into fluent readers had right-lateralized ERPs to deviant tone frequencies or MMRs to CVC syllable changes and at-risk newborns with later reading problems exhibited left-lateralized ERPs to deviant stimuli (Leppänen et al., 2010; Van Zuijen et al., 2013). The lateralization pattern in no-risk newborns in our study extends the dissenting literature on this topic in healthy infants. Future research should aim to clarify whether lateralization is influenced by, for instance, the use of non-speech vs. speech stimuli and the maturation of the auditory system.

The observed distinct MMR topography pattern in no-risk compared with high-risk infants in this study could stem from the cortical locations or orientations of MMR generators. However, this and most of previous infant EEG studies were not designed to estimate MMR sources. Due to a small amount of electrodes used in this study, the above-discussed findings on scalp distributions should be confirmed by studies designed for better source localization, e.g., using additional anatomical MRIs and high-density EEG or magnetoencephalography.

4.5. Summary and conclusions

Our novel results shed light on the nature of speech-processing deficits in newborns at high risk of dyslexia, showing an extensive pattern of atypical speech-sound discrimination in high-risk newborns including absent or weaker MMRs, as well as deviating MMR polarities compared to control newborns. These results, with larger group sizes and a more extensive stimulus set than in previous studies, support and extend previous findings. Irregularities in the neural discrimination of speech at newborn age could result in weak, inaccurate, or slow formation of neural speech-sound representations in the brain, which can be a precursor for impaired language and reading-skill acquisition. The findings of this study can contribute to unravel the early origins of dyslexia. Revealing the neural basis and nature of these speech processing deficits already at birth can assist in the design of targeted interventions to support language development from the beginning of life.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgements

The authors would like to thank research nurses Tarja Ilkka and Svetlana Permi for conducting the majority of the EEG recordings, all research assistants involved in this project for their help, and Prof. Laurel Trainor and Tommi Makkonen, M.Sc. (Tech.), for guidance during data analysis. Finally, we would like to thank all participating families for their motivation and engagement in this longitudinal study. This work was supported by Jane and Aatos Erkko Foundation and the Academy of Finland [project number 276414]. The funding sources were not involved in the planning and execution of the study, nor in the writing of the article and decision to submit.

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Heliyon 6 (2020) e04619

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Neuromagnetic speech discrimination responses are associated with reading-related skills in dyslexic and typical readers

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ARTICLE INFO

Keywords:
Dyslexia
Magnetoencephalography (MEG)
Speech processing
Mismatch field (MMF)
Reading skills
Verbal working memory
Behavioral neuroscience
Cognitive neuroscience
Applied linguistics
Clinical psychology
Cognitive psychology

ABSTRACT

Poor neural speech discrimination has been connected to dyslexia, and may represent phonological processing deficits that are hypothesized to be the main cause for reading impairments. Thus far, neural speech discrimination impairments have rarely been investigated in adult dyslexics, and even less by examining sources of neuromagnetic responses. We compared neuromagnetic speech discrimination in dyslexic and typical readers with mismatch fields (MMF) and determined the associations between MMFs and reading-related skills. We expected weak and atypically lateralized MMFs in dyslexic readers, and positive associations between reading-related skills and MMF strength. MMFs were recorded to a repeating pseudoword */ta-ta/* with occasional changes in vowel identity, duration, or syllable frequency from 43 adults, 21 with confirmed dyslexia. Phonetic (vowel and duration) changes elicited left-lateralized MMFs in the auditory cortices. Contrary to our hypothesis, MMF source strengths or lateralization did not differ between groups. However, better verbal working memory was associated with stronger left-hemispheric MMFs to duration changes across groups, and better reading was associated with stronger right-hemispheric late MMFs across speech-sound changes in dyslexic readers. This suggests a link between neural speech processing and reading-related skills, in line with previous work. Furthermore, our findings suggest a right-hemispheric compensatory mechanism for language processing in dyslexia. The results obtained promote the use of MMFs in investigating reading-related brain processes.

1. Introduction

In developmental dyslexia, which is highly prevalent (up to 17%, Elliot and Grigorenko, 2014) and cumbersome for individuals in modern societies, reading-skill acquisition is compromised despite appropriate education and normal intelligence (Lyon et al., 2003). Dyslexia has been associated with significant difficulties in phonological processing (Laasonen et al., 2010; Ramus, 2001; Ramus et al., 2018), which may result from poor phonological representations or their accessibility (Ramus, 2001; Ramus et al., 2013). A range of other dysfunctions of cognition, such as deficits in working memory, especially verbal short-term memory, are associated with or potentially underlie reading deficits (Banai and Ahissar, 2004; Laasonen et al., 2009).

Dyslexia has been associated with several structural and functional brain abnormalities relevant for speech and language processing (Eckert et al., 2016; Giraud and Poeppel, 2012; Lehongre et al., 2011; Linkersdörfer et al., 2012; Richlan et al., 2013, 2011; 2009; Schulte-Körne et al., 2001). Acoustic–phonological processes pertinent for speech functions can be investigated with mismatch negativity (MMN) responses recorded by electroencephalography (EEG) or magnetoencephalography (MEG; Näätänen, 2001). MMN is an event-related component elicited by rare changes in a stream of repeating sounds (Näätänen et al., 1978), reflecting neural sound discrimination (Kujala and Näätänen, 2010). The primary MMN generators are located in bilateral temporal cortices (e.g., Alho, 1995). The left-hemisphere generator contributes more to speech processing than the right one, presumably reflecting native phonology (e.g., Näätänen et al., 1997; Shestakova et al., 2002; Shtyrov et al., 2000).

MMN is linked with language and reading skills, which makes it a promising neural marker for dyslexia. For example, larger MMN amplitudes to speech-sound changes have been associated with better

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https://doi.org/10.1016/j.heliyon.2020.e04619
Received 13 March 2020; Received in revised form 9 June 2020; Accepted 30 July 2020

phoneme processing skills in typically developing prereaders (Linnavalli et al., 2017) and better scores in pseudoword reading in children with auditory processing disorder (Sharma et al., 2006). This response can also predict future development, as shown by MMNs recorded to speech sounds in kindergarten (Maurer et al., 2009) and in infancy (Van Zuijen et al., 2013) that are associated with language and reading outcomes at school.

In line with this, MMNs to speech-sound and non-speech-sound changes were shown to be diminished and delayed in children and adults with dyslexia (for reviews, see Hämäläinen et al., 2013; Kujala and Näätänen, 2001; Schulte-Körne and Bruder, 2010), and even in infants and children having a familial risk of dyslexia (Benasich et al., 2006; Leppänen et al., 2002; Lovio et al., 2010; Schaadt et al., 2015; Schaadt and Männel, 2019; Schulte-Körne et al., 1998; Thiede et al., 2019; van Leeuwen et al., 2008; for a review, see Ozernov-Palchik and Gaab, 2016). Some studies, however, showed abnormally enhanced MMNs to sound changes in dyslexics (Corbera et al., 2006; Hämäläinen et al., 2008) and in others the MMNs were atypical in dyslexics only for certain stimulus types (Baldeweg et al., 1999; Meng et al., 2005; Schulte-Körne et al., 1998).

The language and speech processing deficits in reading impairments may also be reflected in atypical cerebral lateralization of these functions (Heim et al., 2004; Vandermosten et al., 2013; Zhao et al., 2016; however, see Wilson and Bishop, 2018). MMNs to tone or tone-pattern changes were found to be abnormally lateralized in dyslexia (Kujala et al., 2003; Kujala et al., 2000; Renvall and Hari, 2003; Sebastian and Yasin, 2008; see, however, Kujala et al., 2006; Schulte-Körne et al., 1999, 2001; Sharma et al., 2006). However, only few studies have investigated lateralization of speech-elicited MMNs in dyslexia or at-risk groups, with mixed results. For example, one study found left-lateralized MMN to phoneme changes in kindergarten to predict good reading skills and right-lateralized MMN poor reading skills at school (Maurer et al., 2003), whereas other studies reported no lateralization differences in the speech-elicited MMN between dyslexic and control groups (Schulte-Körne et al., 2001; Sebastian and Yasin, 2008).

Very few MMN studies on dyslexia have so far used spatially accurate methods to determine response strengths or lateralization. One such method is MEG which has better spatial resolution but the same excellent temporal resolution than EEG. Renvall and Hari (2003), utilizing MEG, reported weaker left-hemispheric mismatch fields (MMFs, used here, also called magnetic mismatch negativity, MMNm, the magnetic equivalent of MMN) to tone frequency changes in adult dyslexic than non-dyslexic readers. To our knowledge, the only previous study comparing MMFs in dyslexic and control children to speech-sound changes (*/ba/* vs. */da/*) failed to find group differences (Paul et al., 2006). The present MEG study addresses this apparent niche in dyslexia research. We also refined the spatial accuracy of MEG by applying individual head models from anatomical MRIs for MMF source localizations. To our knowledge, this is the first study investigating MMFs to phonetic changes in dyslexic adults and determining their association with neurocognitive language-related measures.

The present study aimed to investigate neural speech-sound discrimination in dyslexia with spatially accurate source estimates, and its association with reading-related skills. To this end, we recorded MMFs to several speech-sound changes (vowel, vowel duration, syllable frequency) in a phonotactically legal pseudoword and compared their source strengths and latencies between typical and dyslexic readers. Furthermore, we used an extensive neuropsychological test battery tapping reading and related skills (phonological processing, working memory) as well as intelligence quotient (IQ) of the participants. Since earlier studies have shown diminished and delayed MMN amplitudes in dyslexia (for reviews, see Hämäläinen et al., 2013; Kujala and Näätänen, 2001; Schulte-Körne and Bruder, 2010), our first hypothesis was that the dyslexic group exhibits diminished and/or delayed MMF source amplitudes. Secondly, based on previous MMN/MMF studies with tone stimuli in dyslexia (e.g., Kujala et al., 2003; Renvall and Hari, 2003), we hypothesized that the MMFs of the dyslexic group are less lateralized to the left hemisphere. As left-hemispheric MMN generators presumably reflect native phonology (e.g., Näätänen et al., 1997; Shestakova et al., 2002; Shtyrov et al., 2000), we hypothesized that they are also relevant for reading skills. Specifically, the third hypothesis was that better outcomes in all three reading-relevant skills correlate with stronger MMF source amplitudes in both groups, predominantly in the left hemisphere for phonetic changes, i.e., for vowel duration and vowel identity changes.

2. Material and methods

2.1. Participants

Forty-three healthy Finnish participants (21 dyslexics, 22 controls) aged 19–45 years without history of neurological diseases participated in the study. The inclusion criteria for the dyslexic group were a diagnostic dyslexia statement (from a psychologist, special education teacher or similar), or a history of reading difficulties in childhood (see Section 2.2) combined with below-norm performance in either speed or accuracy (below one standard deviation from age-matched standardized control data, see Laasonen et al., 2010) in two or more reading subtests (word list reading, pseudoword list reading, text reading, Nevala et al., 2006). Inclusion criteria for control participants were no report of dyslexia or co-occurring language disorders confirmed by within-norm performance in speed and accuracy in at least two reading subtests. General exclusion criteria were an individualized school curriculum (i.e., individualized education program due to special education needs) or attention deficit disorders (see Section 2.2), oral language development problems indicative of developmental language disorder, performance IQ below 80, and metal in the body. Participants gave their written informed consent, and all procedures employed conformed to the Declaration of Helsinki. The Coordinating Ethics Committee (Hospital District of Helsinki and Uusimaa) approved the study protocol. The study has been pre-registered in clinicaltrials.gov (ID NCT02622360).

2.2. Questionnaires and neuropsychological test battery

All participants filled questionnaires before brain imaging measurements including the Finnish versions of The Adult Reading History Questionnaire (ARHQ; Laasonen et al., 2014) and The Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005). Questionnaires were paired with clinical diagnostic interviews that enquired about past and current reading difficulties and dyslexia in relatives. The interviews also included questions assessing the exclusion criteria, such as those concerning broader cognitive deficits, oral language development problems and attention-related deficits. The neuropsychological tests were grouped into domains of technical reading, phonological processing, working memory, and intelligence. Technical reading (as opposed to reading comprehension in text reading that was used for dyslexia assessments, see Section 2.1) was assessed with word-list reading and pseudoword-list reading (speed and accuracy, Nevala et al., 2006). Phonological processing was assessed with a Nonword span test, in which participants repeated a lengthening sequence of nonwords (span length, Laasonen, 2002), the Pig Latin test, in which participants had to change the first syllables between two pseudowords (e.g., kouta – mesi rebuilds to meuta – kosi, accuracy, Nevala et al., 2006), and rapid alternate stimulus naming, in which changing stimuli (colours, number, letters) had to be named fast and accurately (RAS, speed in second trial, Wolf, 1986). Working memory was assessed with the Wechsler Memory Scale III (WMS-III, Wechsler, 2008) including visual working memory (subtest Visual Series) and verbal working memory (Number Series). Intelligence was assessed with the Wechsler Adult Intelligence Scale IV (Wechsler, 2005) including verbal IQ (Similarities and Vocabulary), performance IQ (Block Design and Matrix Reasoning), and full IQ (all four previous subtests). Composite scores were computed for phonological processing and technical reading by converting the raw scores of all subtests to

z-scores and averaging them, and for working memory functions by following the procedure advised in WMS-III.

The control group outperformed the dyslexic group in technical reading, phonological processing, working memory, as well as in verbal IQ, as expected (Table 1, Figure 1). However, the control group also had a higher performance IQ and higher education than the dyslexic group. As dyslexic readers are known to underperform in verbal, but not necessarily in performance IQ (Laasonen et al., 2009), the performance IQ was taken into account in the correlation analysis as a control variable, and analyses including group comparisons were repeated with groups matched for performance IQ (see 2.7).

2.3. Stimuli

The repetitive "standard" stimulus was a naturally recorded Finnish 300-ms-long pseudoword */ta-ta/* with the stress on the first syllable (Pakarinen et al., 2014; Thiede et al., 2019). Occasional "deviant" stimuli included a change in vowel duration (lengthening of second */a/* of the standard stimulus from 71 to 158 ms), vowel identity (adding */o/* to the second syllable from a natural recording of */ta-to/*, pitch-controlled), or syllable frequency (shifting the f_0 of the second syllable from 175 to 225 Hz) in the second syllable (edited with Adobe Audition CS6, 5.0, Build 708 and Praat 5.4.01). The duration of the vowel identity and syllable frequency deviants was identical to the duration of the standard stimulus. The intensity level of all deviants was root-mean-square normalized to match the average intensity level of the standard stimulus. The onset of change was at 180 ms from stimulus onset for the frequency and vowel deviants, and at 225 ms from stimulus onset for the duration deviant. Stimuli were presented pseudo-randomly (at least one standard always following a deviant) in two ≈12.6 min recording blocks, each containing 946 stimuli and starting with five standard stimuli. Standards were presented with a probability of approximately 75.3% and each deviant type with a probability of 8.3%. The stimulus-onset asynchrony (SOA) was 800 ± 50 ms (randomly alternating between 750, 760, 770, …, 840, 850 ms).

The stimuli were presented during MEG/EEG recordings with Presentation Software (Neurobehavioural Systems Ltd., Berkeley, CA, USA) binaurally via plastic tubes and silicon earphones at a comfortable level (≈70–80 dB SPL). During stimulation, participants were sitting, instructed to keep the head still and to attend to a self-selected, subtitled, and silenced movie projected (Panasonic PT-D7500E; Panasonic, Kadoma, Osaka, Japan) to a back-projection screen (MEGIN Oy, Helsinki, Finland) located 150 cm from the participant's head.

2.4. MEG/EEG and MRI procedure

MEG/EEG was recorded using a 306-channel Elekta Neuromag TRIUX (MEGIN Oy, Helsinki, Finland) whole-head MEG system (sampling rate 1 kHz and pass-band 0.03–330 Hz) in a magnetically shielded room (Euroshield/ETS Lindgren Oy, Eura, Finland) in BioMag Laboratory in Helsinki University Central Hospital (duration 2–3 h). Prior to the measurement, the positions of five head position indicator (HPI) coils and additional head surface points (EEG electrodes) were determined in relation to the nasion and both preauricular points with an Isotrak 3D-digitizer (Polhemus Inc., Colchester, USA). The head position with respect to the MEG sensor array was continuously monitored. Vertical and horizontal electro-oculograms (EOG) were recorded.

The anatomical T1-weighted images (MPRAGE) were acquired on a 3T MAGNETOM Skyra whole-body MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil at AMI centre of Aalto Neuroimaging (duration 30 min), Aalto University (176 slices, slice thickness 1 mm, voxel size 1 mm × 1 mm × 1 mm, field of view 256 mm × 256 mm). The images were checked for incidental findings by a physician.

2.5. Data preprocessing

The following processing steps were executed in MNE-Python software package v0.17.dev0 (Gramfort et al., 2014), unless indicated otherwise; the code is available at https://github.com/athiede13/neural_sources. Temporal signal space separation (tSSS; Taulu and Simola, 2006) with head movement compensation and interpolation of previously marked bad channels was performed with Maxfilter software (version 2.2.15; MEGIN Oy, Helsinki, Finland). Ocular and cardiac artifacts were removed by signal space projection (SSP; Tesche et al., 1995). The data were filtered to 0.5–30 Hz with a finite impulse response filter, and epochs were extracted 100 ms before and 840 ms after stimulus onset for all stimulus types for all channels and each participant and recording. Epochs with signal excursion exceeding 4 pT in magnetometers, 4 pT/cm in gradiometers and 250 μV in EOG channels were excluded from analysis. For the standard stimuli, on average 679 epochs (range 667–681) per participant were included in the analysis. For the frequency, duration, and vowel deviants, on average 144 (139–146), 145 (142–147), and 142 epochs (138–144), respectively, were included in the analysis per participant. Deviant-minus-standard subtraction curves (MMFs) were calculated for each deviant type with equal weights.

The anatomical MRI of each participant was preprocessed with Freesurfer software (http://surfer.nmr.mgh.harvard.edu/) version 5.3

Table 1. Demographic and neuropsychological characterization of the study groups.

Variable	CON (N = 22)	DYS (N = 21)	Comparison		
			test statistic	*p*	95% confidence interval
Demographic					
gender [f/m]	12/10	12/9	$X^2(1) = 0$	1	
age [years]	29.9 (5.9)	31.0 (8.6)	$t(35) = -0.48$	.633	[-5.68 3.50]
education [years]	17.0 (2.5)	14.7 (2.5)	$t(40) = 3.06$	.004	[0.80 3.93]
music education# [years]	0.25 (5.5)	0.0 (2.0)	W = 283.5	.152	
Neuropsychological					
full IQ	117.0 (7.0)	104.0 (9.4)	t(37) = 5.18	$8.0*10^{-6}$	[8.00 18.26]
verbal IQ#	115.0 (10.0)	100.0 (22.0)	W = 390.5	$1.0*10^{-4}$	
performance IQ	120.0 (10.0)	110.0 (12.3)	t(39) = 3.13	.003	[3.77 17.61]
phonological processing	0.49 (0.42)	-0.33 (0.60)	t(36) = 5.18	$8.9*10^{-6}$	[0.50 1.14]
technical reading#	0.61 (0.17)	-0.34 (0.82)	W = 461	$3.8*10^{-12}$	
working memory	24.3 (4.8)	19.8 (5.0)	t(41) = 3.01	.004	[1.49 7.53]

Notes. Mean and standard deviation (in brackets) for normally-distributed variables (Shapiro-Wilk test). Group comparison with independent-samples t-test. Median and interquartile range (in brackets) for non-normally-distributed variables, indicated by the hash sign#. Group comparison with Wilcoxon Rank Sum W-test. Test statistics, degrees of freedom (in brackets), significance levels *p*, and 95% confidence intervals are reported. CON – control group, DYS – dyslexic group.

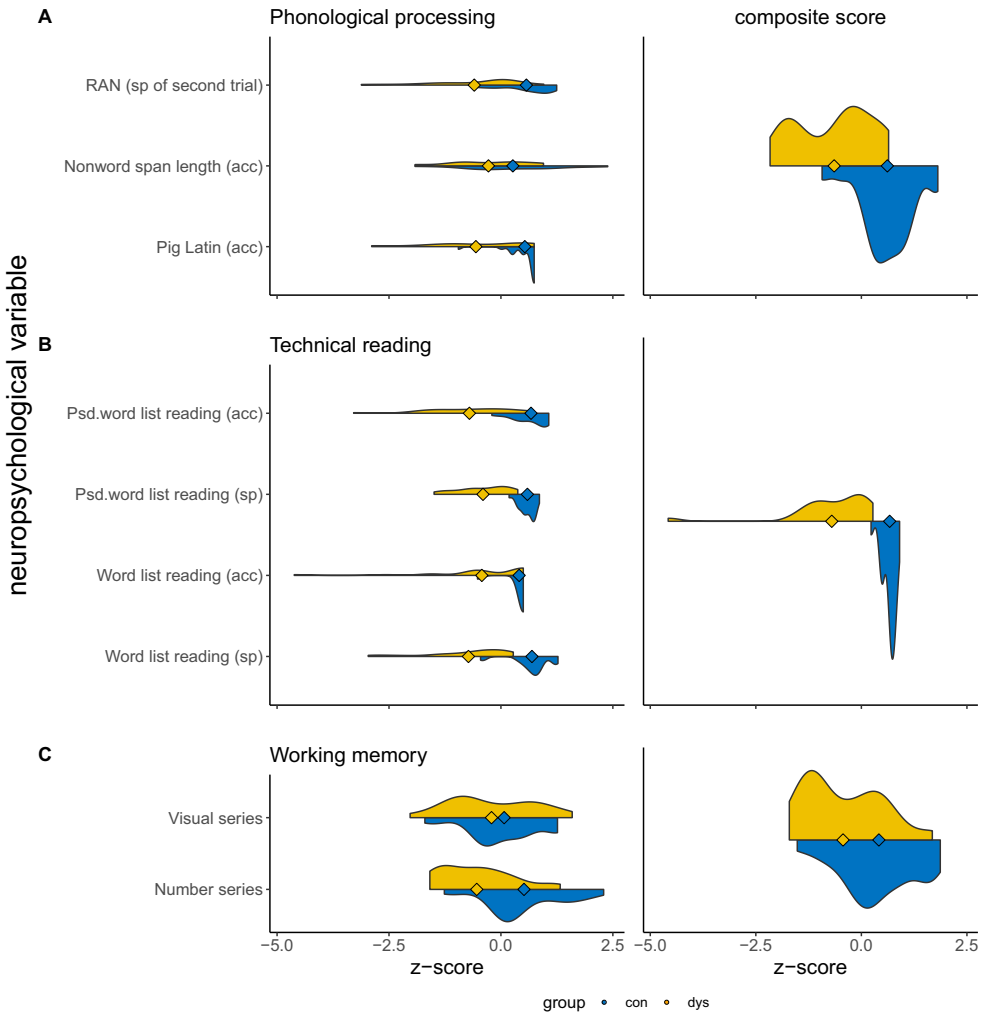

Figure 1. Neuropsychological profiles of the participants visualized by violin plots (blue – control group, yellow – dyslexic group). Means of group distributions are indicated by a diamond shape. Single variables are shown on the left and composite scores on the right panels. A) Phonological processing. B) Technical reading. C) Working memory. sp - speed, acc - accuracy, psd - pseudo.

and 6.0 following the standard procedure (Fischl, 2012). Manual editing of pial surface and white matter control points (64% and 18% of cases, respectively) ensured a correct segmentation of the cortex.

2.6. Source modeling

After MRI–MEG coregistration (*mne coreg*), the generators of individual MMFs were estimated in a cortically-constrained source space; the MEG forward solution was calculated for 4098 source points per hemisphere. The minimum-norm source estimate (MNE) was computed for the MMFs using depth-weighting (0.8), fixed-orientation constraint, and the 100-ms-pre-stimulus-baseline regularized noise covariance of pooled deviant and standard waveforms of each participant. The MNE source estimates were morphed to Freesurfer's average subject (*fsaverage*) cortical space and averaged for each group.

Auditory cortices (lateral sections of superior temporal gyrus and sulcus of the Destrieux Atlas, aparc.a2009s in Freesurfer, Destrieux et al., 2010) were *a priori* chosen as regions of interest (ROI) based on previous research (Alho, 1995; Renvall and Hari, 2003). As this region is considerably larger than the presumed region generating MMF, the average of the dipole moments within that ROI is not representative of the activity of interest. Therefore, data-driven functional ROIs were created based on the MNE source estimate of each participant for each MMF at the individual peak time within the MMF time window (see below). Specifically, the functional ROIs were created by taking the top 60% of individual peak source estimates within the anatomical *a priori* -defined ROI and then combined into one for the most consistent individual source points (in more than 45% of all functional ROIs) to represent the area with the most consistent activity across participants. The source time course at the functional ROI were extracted with source signs flipped depending on the source orientation (*pca_flip*) to avoid cancellation.

Time windows for determining the maximum MMF source amplitudes and latencies were selected around the visually inspected peaks of the averages across all participants and deviant types, groups combined, resulting in a 100-ms wide window for the first peak (120–220 ms after change onset for frequency and vowel deviant, 75–175 ms after change onset for duration deviant) and a 200-ms wide window for the second peak (270–470 ms after change onset for frequency and vowel deviant, 225–425 ms after change onset for duration deviant). Individual maximum amplitudes and the corresponding latencies were extracted within the determined time windows and ROI for statistical analysis in both hemispheres.

2.7. Statistical analysis

SPSS version 25.0.0.1 (IBM, Armonk, New York, USA), R (R Core Team, 2018) and RStudio version 1.1.453 (RStudio Team, 2016) were used for statistical analyses. To validate that MMFs were elicited in the

selected time windows in both groups, MMF source amplitudes (difference waveforms) were tested for statistical significance with one-sample *t*-tests against zero separately in each group. Group and laterality effects and their interactions on MMF source amplitudes (difference waveforms) were analyzed with three-way repeated-measures analysis of variance (ANOVA) with group (control, dyslexic) as between-subjects factor and laterality (left, right), deviant (frequency, duration, vowel), and time (MMF, late MMF) as within-subjects factors. Group and laterality effects and their interactions on MMF source latencies were analyzed with two-way repeated-measures ANOVAs with group as between-subjects factor and laterality and deviant as within-subjects factors. In the ANOVAs, main effects of deviant or time were not investigated. Significant three-way interactions were further investigated with separate follow-up ANOVAs. Greenhouse-Geisser correction was applied when the sphericity assumption was violated. Bonferroni correction was used to account for multiple comparisons in all *post-hoc* tests and only corrected *p*-values are reported. Although performance IQ differed between the groups, an analysis of covariance with performance IQ as a covariate was not performed, following the recommendations of Dennis et al. (2009). Instead, to ensure that the IQ difference would not explain the results, statistical analyses comparing groups were repeated for a sample in which the groups were matched for performance IQ ($N = 37$, 19 in control group, 18 in dyslexic group). The profile of the matched groups did not otherwise differ from the original sample.

Partial Pearson correlations were computed between MMF source amplitudes and neuropsychological test scores, controlling for the effect of performance IQ. In order to reduce the amount of tests, correlations were analyzed in three steps both separately for the two groups and across groups; (1) for MMF source amplitudes at two hemispheres averaged across all deviants with the three neuropsychological composite scores, if significant, then (2) separately for MMFs to each deviant, if significant, then (3) separately for each subcomponent of the neuropsychological composite scores. Despite a potential risk of circular inference (Kriegeskorte et al., 2009), this stepwise procedure was chosen to output the most meaningful associations from a neuroscientific and neuropsychological perspective. Bonferroni correction for multiple comparisons was employed at each step, as recommended by Rousselet and Pernet (2012).

3. Results

The MMF source waveform (difference waveform) indicated two responses (Figure 2), referred to as MMF and late MMF (peaking at 125–170 ms and 325–370 ms from change onset, respectively) that were both significantly larger than zero in both groups and for all deviants (amplitude range 15–44 pAm; Table 2). Their peak activations were located in the left middle temporal cortex (BA21 and BA22) and in the right superior temporal cortex (BA41 and BA22; Figure 2).

Full statistics of significant effects in all ANOVAs and *post-hoc* analyses are reported in Table 3. A significant main effect was found for laterality, indicating larger left- than right-hemispheric responses. A significant two-way interaction effect was found between laterality and deviant, as well as time and deviant. A significant three-way interaction effect between laterality, deviant, and time was also found for the MMF source amplitudes (difference waveforms). A follow-up ANOVA for the MMF time windows revealed a significant laterality main effect, indicating larger left- than right-hemispheric responses. A significant interaction effect was found between laterality and deviant for the MMF time window. *Post-hoc* analysis of that interaction indicated larger left- than right-hemispheric MMFs to the vowel deviant. A follow-up ANOVA for the late MMF time window revealed a significant main effect of laterality, indicating larger left- than right-hemispheric responses.

For the late MMF source latencies, a significant interaction effect between laterality and group was found, indicating slower late MMFs in the left than right hemisphere in the control group only. The reported ANOVA results remained similar when repeating the analyses for performance-IQ-matched subsamples of control and dyslexic groups; only the latter effect on late MMF latencies disappeared (Table 4).

Source amplitudes of MMF and late MMF correlated with neuropsychological test scores (Figure 3, Table 5). Larger MMF source amplitudes in the left hemisphere were weakly correlated ($r = .25$; $p = .03$) with better working memory skills across all deviants and across both groups.

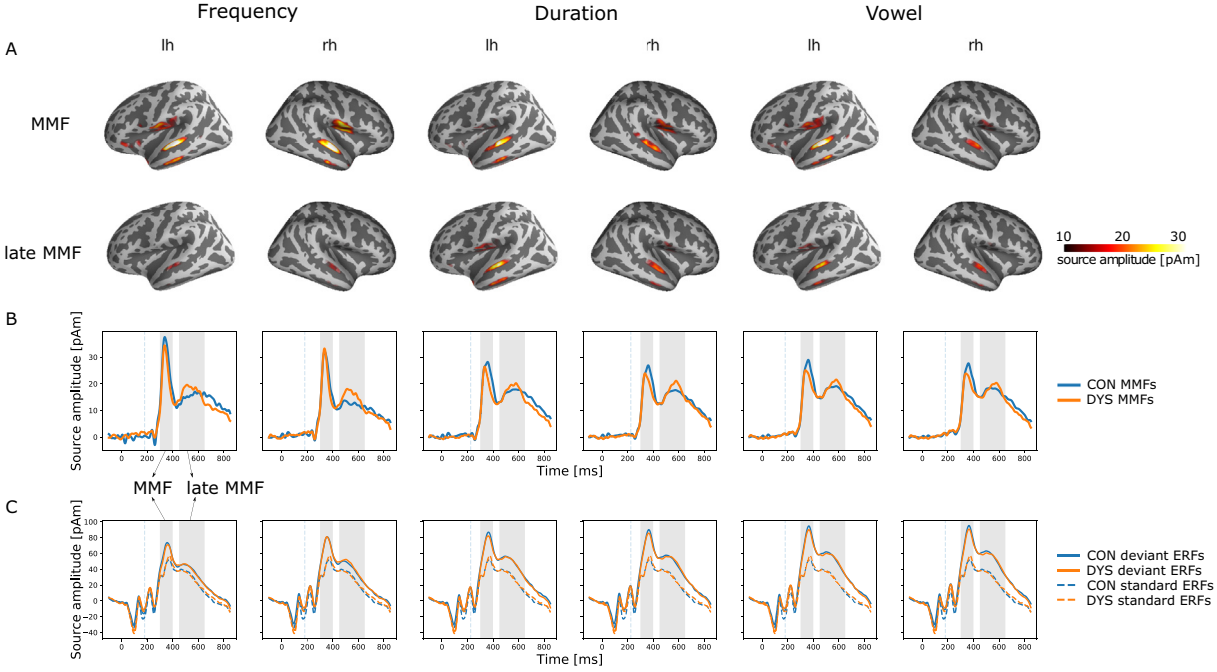

Figure 2. Neural sources of MMF and late MMF to frequency, duration, and vowel changes. A) Source locations as MNE's on lateral brain surfaces. B) Extracted ROI time courses (subtraction curves, i.e. MMFs and late MMFs). C) Event-related fields (ERFs) to standard and deviant (frequency, duration, and vowel deviants) stimuli extracted from the same ROI. Grey shaded areas in ROI time courses (B and C) depict the time windows of interest (first – MMF, second – late MMF) and dotted vertical lines represent the change onset. lh – left hemisphere, rh – right hemisphere, CON – control group, DYS – dyslexic group.

Table 2. Descriptive statistics (mean M, standard deviation SD) of maximal source amplitudes and one-sample t-test results for significance testing against zero (with confidence interval CI).

Deviant	Group	Hemi	Descriptives		One-sample *t*-test			
			M [pAm]	*SD* [pAm]	*t*	*df*	*p*	95% *CI*
MMF								
fre	con	lh	44	20	10.04	21	<.001	[35 53]
		rh	33	17	9.21	21	<.001	[26 41]
	dys	lh	39	14	12.92	20	<.001	[32 45]
		rh	36	20	8.30	20	<.001	[27 45]
dur	con	lh	38	22	8.29	21	<.001	[29 48]
		rh	31	11	13.90	21	<.001	[26 36]
	dys	lh	26	11	10.58	20	<.001	[21 32]
		rh	30	18	7.76	20	<.001	[22 38]
vow	con	lh	42	21	9.15	21	<.001	[32 51]
		rh	26	14	9.18	21	<.001	[20 32]
	dys	lh	37	14	11.87	20	<.001	[31 44]
		rh	25	15	7.98	20	<.001	[19 32]
late MMF								
fre	con	lh	23	17	6.59	21	<.001	[16 31]
		rh	15	20	3.64	21	.002	[7 24]
	dys	lh	24	12	9.41	20	<.001	[19 30]
		rh	20	20	4.50	20	<.001	[11 29]
dur	con	lh	37	10	17.81	21	<.001	[33 41]
		rh	25	14	8.54	21	<.001	[19 31]
	dys	lh	32	14	10.25	20	<.001	[26 39]
		rh	26	15	8.06	20	<.001	[20 33]
vow	con	lh	33	14	11.23	21	<.001	[27 39]
		rh	22	18	5.70	21	<.001	[14 30]
	dys	lh	32	10	14.46	20	<.001	[27 36]
		rh	20	18	4.95	20	<.001	[11 28]

Table 3. Significant ANOVA effects (N = 43).

		Model	ANOVA						*post-hoc*						
			effect	*F*	*df1*	*df2*	*p*	η_p^2	effect	*EMM1*	*(SEM1)*		*EMM2*	*(SEM1)*	*p*
AMPLITUDES		laterality * deviant * time * group	laterality	9.48	1.00	41	.004	.19	left > right	34	(2)	>	26	(2)	
			time	30.49	1.00	41	<.001	.43	MMF > late MMF	34	(2)	>	26	(1)	
			laterality * deviant	5.44	2.00	82	.006	.12	not tested, due to three-way interaction effect						
			deviant * time	39.52	1.65	82	<.001	.49	not tested, due to three-way interaction effect						
			laterality * deviant * time	4.75	2.00	82	.011	.10	separate ANOVAs for the two time windows (below), due to several significant pairwise comparisons						
	MMF	laterality * deviant * group	laterality	6.89	1.00	41	.024	.14	left > right	38	(2)	>	30	(2)	
			deviant	9.03	2.00	82	.001	.18	not tested, due to interaction effect						
			laterality * deviant	7.91	2.00	82	.001	.16	vow: left > right	40	(3)	>	26	(2)	<.001
									left: fre > dur	41	(3)	>	32	(3)	<.001
									left: vow > dur	40	(3)	>	32	(3)	.003
									right: fre > vow	35	(3)	>	26	(2)	.003
	late MMF	laterality * deviant * group	laterality	9.41	1.00	41	.008	.19	left > right	30	(2)	>	21	(2)	.004
			deviant	14.98	2.00	82	<.001	.27	fre < dur	21	(2)	<	30	(2)	<.001
									fre < vow	21	(2)	<	27	(2)	.005
LATENCIES	MMF	laterality * deviant * group	deviant	34.65	2.00	82	<.001	.46	fre < dur	340	(2)	<	368	(3)	<.001
									fre < vow	340	(2)	<	360	(3)	<.001
	late MMF	laterality * deviant * group	deviant	7.59	2.00	82	.001	.16	fre < dur	534	(6)	<	561	(7)	.007
									vow < dur	534	(6)	<	561	(7)	.011
			laterality * group	4.46	1.00	41	.041	.10	con: left > right	555	(10)	>	526	(8)	.010

Notes: *p*-values are Bonferroni-corrected for all *post-hoc* analyses, i.e., for separate ANOVAs for the two time windows (two latter ANOVAs for amplitudes) and all *p*-values on the right-most column. EMM and SEM for analyses referring to amplitudes are in pAm and for analyses referring to latencies in ms. fre – frequency, dur – duration, vow – vowel, con – control group, η_p^2 – effect size (partial eta squared), EMM – estimated marginal means, SEM – standard error of means.

Table 4. Significant ANOVA effects (N = 37).

		Model	ANOVA						Post-hoc						
			effect	*F*	*df1*	*df2*	*p*	η_p^2	effect	*EMM1*	*(SEM1)*		*EMM2*	*(SEM1)*	*p*
AMPLITUDES		laterality * deviant * time * group	laterality	6.90	1.00	35	.013	.16	left > right	34	(2)	>	26	(2)	
			time	36.42	1.00	35	<.001	.51	MMF > late MMF	34	(2)	>	25	(2)	
			laterality * deviant	4.56	2.00	70	.014	.12	not tested, due to three-way interaction effect						
			deviant * time	34.69	1.66	70	<.001	.50	not tested, due to three-way interaction effect						
			laterality * deviant * time	4.97	2.00	70	.010	.12	separate ANOVAs for the two time windows (below), due to several significant pairwise comparisons						
	MMF	laterality * deviant * group	deviant	7.51	2.00	70	.002	.18	not tested, due to interaction effect						
			laterality * deviant	7.49	2.00	70	.002	.18	vow: left > right	40	(3)	>	26	(2)	<.001
									left: fre > dur	42	(3)	>	32	(3)	<.001
									left: vow > dur	40	(3)	>	32	(3)	.004
									right: fre > vow	35	(3)	>	26	(2)	.008
	late MMF	laterality * deviant * group	laterality	7.09	1.00	35	.023	.17	left > right	30	(2)	>	21	(3)	.012
			deviant	13.65	2.00	70	<.001	.28	fre < dur	20	(2)	<	29	(2)	<.001
									fre < vow	20	(2)	<	26	(2)	.002
LATENCIES	MMF	laterality * deviant * group	deviant	2.00	70.00	30	<.001	.46	fre < dur	340	(2)	<	368	(3)	<.001
									fre < vow	340	(2)	<	360	(3)	<.001
	late MMF	laterality * deviant * group	deviant	2.00	70.00	7	.001	.17	fre < dur	533	(7)	<	562	(8)	.009
									vow < dur	534	(7)	<	562	(8)	.017

Notes: *p*-values are Bonferroni-corrected for all *post-hoc* analyses, i.e., for separate ANOVAs for the two time windows (two latter ANOVAs for amplitudes) and all *p*-values on the right-most column. EMM and SEM for analyses referring to amplitudes are in pAm and for analyses referring to latencies in ms. fre – frequency, dur – duration, vow – vowel, con – control group, η_p^2 – effect size (partial eta squared), EMM – estimated marginal means, SEM – standard error of means.

Separate correlation tests for the deviants revealed a moderate correlation across groups for the left duration MMF with working memory skills (r = .40; p = .024). Separate working memory subtest analysis (visual and verbal) only showed a significant moderate correlation between the left duration MMF and the verbal working memory component (r = .46; p = .006). Within the control group, left MMFs across all deviants correlated moderately (r = .37; p = .015) with working memory skills. In separate tests for the deviants, the left MMF for the duration deviant was significant when uncorrected, but did not remain significant after Bonferroni correction. Within the dyslexic group, larger right MMFs (only uncorrected) and right late MMFs (also significant after corrections) across all deviants correlated moderately strongly (r = .36; p = .028) with better technical reading skills. In separate tests for the deviants, none remained significant.

4. Discussion

Our goals were to determine whether neural speech-sound discrimination is deficient or abnormally lateralized in adult dyslexic readers, and whether the speech-elicited neural responses correlate with reading-related skills. To improve spatial accuracy from previous EEG studies we recorded MMFs with MEG, and utilized individual MRIs for source

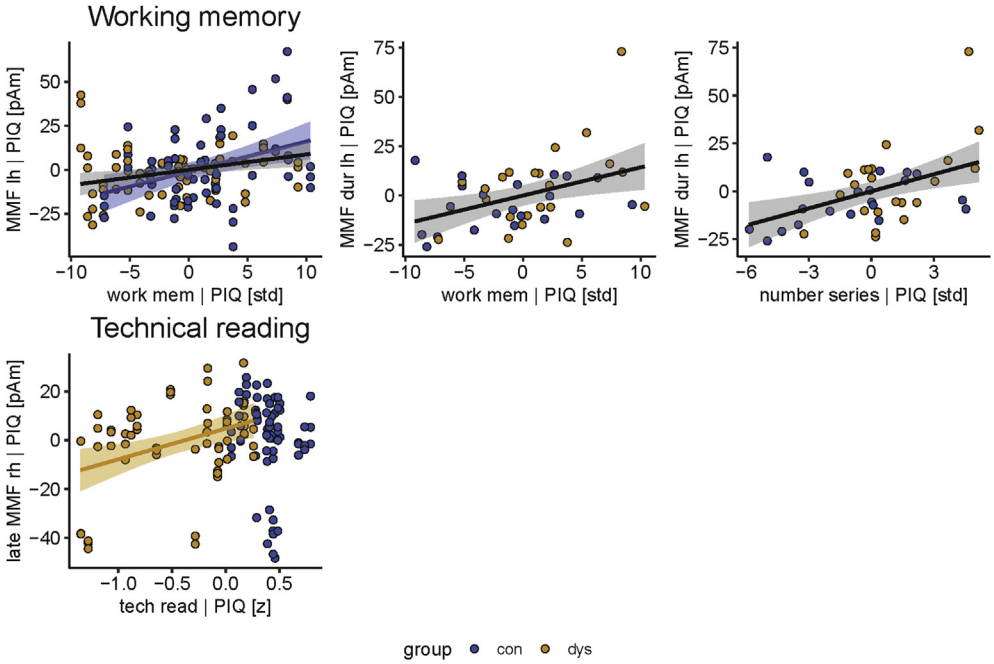

Figure 3. Significant partial Pearson correlations after Bonferroni correction of MMF and late MMF amplitudes with reading-related skills controlled for performance IQ. Scatter plots with linear regression lines (black – across both groups, blue – control group, yellow – dyslexic group) are shown for both all deviants pooled together (upper left and bottom panel) and separately for one deviant (upper middle and right panels). Number series is one subcomponent of the working memory composite score (upper right panel). One outlier (dyslexic) was removed, because of the technical reading score being below three interquartile ranges. work mem – working memory, tech read – technical reading, lh – left hemisphere amplitude, rh – right hemisphere amplitude, PIQ – performance IQ.

Table 5. Partial Pearson correlations of MMF source amplitudes with neuropsychological tests controlled for performance IQ.

	comp.	deviant	correlation	p_{uncorr}	p_{corr}	*signif.*	*r*
both groups pooled (N = 43)	**1a) correlations of lh & rh amplitudes for all deviants pooled with three composite scores (*df* = 126)**						
	MMF	all	lh ~ phon	0.058	0.350		0.17
			rh ~ phon	0.441	2.648		-0.07
			lh ~ read	0.110	0.657		0.14
			rh ~ read	0.327	1.962		0.09
			lh ~ work mem	**0.005**	**0.030**	*	**0.25**
			rh ~ work mem	0.832	4.995		-0.02
	late MMF	all	lh ~ phon	0.429	2.573		0.07
			rh ~ phon	0.782	4.692		0.02
			lh ~ read	0.311	1.864		0.09
			rh ~ read	0.057	0.341		0.17
			lh ~ work mem	0.111	0.665		0.14
			rh ~ work mem	0.223	1.336		0.11
	1b) correlations of lh amplitudes for deviants separately with working memory (*df* = 40)						
	MMF	frequency	lh ~ work mem	0.429	1.287		0.13
		duration	**lh ~ work mem**	**0.008**	**0.024**	*	**0.40**
		vowel	lh ~ work mem	0.156	0.469		0.22
	1c) correlations of lh amplitudes of duration MMF with subcomponents of working memory (*df* = 40)						
	MMF	**duration**	**lh ~ number series**	**0.002**	**0.006**	**	**0.46**
			lh ~ visual series	0.117	0.352		0.25
control group (N = 22)	**2a) correlations of lh & rh amplitudes for all deviants pooled with three composite scores (*df* = 63)**						
	MMF	all	lh ~ phon	0.011	0.069		0.31
			rh ~ phon	0.407	2.439		0.10
			lh ~ read	0.051	0.307		-0.24
			rh ~ read	0.209	1.256		-0.16
			lh ~ work mem	**0.003**	**0.015**	*	**0.37**
			rh ~ work mem	0.327	1.963		0.12
	late MMF	all	lh ~ phon	0.860	5.159		0.02
			rh ~ phon	0.822	4.931		0.03
			lh ~ read	0.124	0.745		-0.19
			rh ~ read	0.491	2.947		-0.09
			lh ~ work mem	0.085	0.508		0.22
			rh ~ work mem	0.247	1.480		0.15
	2b) correlations of lh amplitudes for deviants separately with working memory (*df* = 19)						
	MMF	frequency	lh ~ work mem	0.122	0.367		0.35
		duration	lh ~ work mem	0.037	0.111		0.46
		vowel	lh ~ work mem	0.169	0.507		0.31
dyslexic group (N = 21)	**3a) correlations of lh & rh amplitudes for all deviants pooled with three composite scores (*df* = 60)**						
	MMF	all	lh ~ phon	0.843	5.058		-0.03
			rh ~ phon	0.164	0.986		-0.18
			lh ~ read	0.155	0.928		0.19
			rh ~ read	0.042	0.253		0.27
			lh ~ work mem	0.770	4.622		0.04
			rh ~ work mem	0.440	2.642		-0.10
	late MMF	all	lh ~ phon	0.455	2.728		0.10
			rh ~ phon	0.909	5.452		-0.01
			lh ~ read	0.436	2.615		0.10
			rh ~ read	**0.005**	**0.028**	*	**0.36**
			lh ~ work mem	0.969	5.813		0.01
			rh ~ work mem	0.894	5.364		0.02
	3b) correlations of rh amplitudes for deviants separately with technical reading (*df* = 17)						
	late MMF	frequency	rh ~ read	0.059	0.178		0.44
		duration	rh ~ read	0.251	0.752		0.28
		vowel	rh ~ read	0.110	0.329		0.38

Notes. Reported are partial Pearson correlations. Row is **bolded,** when Bonferroni-corrected significance levels are at $p_{corr} < .05$. One outlier (dyslexic) was removed, because of the technical reading score being below three interquartile ranges. lh – left hemisphere amplitude, rh – right hemisphere amplitude, phon – phonological processing skills, read – technical reading score, work mem – working memory score, acc – accuracy.

localization. We found MMFs and late MMFs from bilateral auditory cortices to all three speech-sound changes. Furthermore, the MMFs and late MMFs were left-lateralized to all three deviants. For the MMFs, the effect was driven by the vowel deviant. Contrary to our expectations, MMFs and late MMFs did not differ in source amplitudes, latencies, or lateralization between dyslexic and typical readers. However, the MMFs were associated with skills pertinent for reading that are known to be affected by dyslexia (D'Mello and Gabrieli, 2018). Correlations were found between stronger left-hemispheric MMFs to the duration deviant and better verbal working memory skills in both groups pooled, and between stronger right-hemispheric late MMFs across deviants and more accurate and faster reading in the dyslexic group. This highlights the functional role of speech-related brain activity in reading and its impairments and promotes the utilization of the auditory MMF as a potential neural marker of abnormal reading.

4.1. MMF, late MMF and speech-sound discrimination

Two response components were found: The MMF peaked at around 125–170 ms after change onset with a clear and narrow peak. This latency is well within the established time range of the MMN/MMF (Kujala et al., 2007). An additional broader, smaller response (late MMF) peaked at around 325–370 ms. A similar response, the late MMN, has been reported in children (Cheour et al., 2001; Volkmer and Schulte-Körne, 2018), but rarely in adults (around 340–600 ms; Hill et al., 2004; Hommet et al., 2009; Korpilahti et al., 1995; Schulte-Körne et al., 2001; Zachau et al., 2005). Its functional role is still poorly understood. It was proposed to reflect linguistic processes as it was elicited by vowel but not by tone changes (Hill et al., 2004; Korpilahti et al., 1995). Late MMNs can, however, be elicited by simple and complex tone changes as well (Schulte-Körne et al., 2001; Zachau et al., 2005). The associations obtained between stronger late MMF in the right hemisphere and more accurate and faster reading-related skills in the dyslexic group support its relevance for linguistic processes in dyslexia. However, the nature of this response remains to be investigated in more detail by future studies.

The MMFs and late MMFs in both groups originated from primary and secondary auditory cortices (peak MNI coordinates corresponded to BAs 41, 21, 22), confirming the findings of previous MMN localization studies applying other types of source modeling (Alho, 1995; Escera et al., 2000). Furthermore, the obtained left-hemispheric lateralization of MMFs to vowel deviants is in line with previous MMF studies on speech processing (e.g., Näätänen et al., 1997; Shtyrov et al., 2000). Late MMFs in the current study were left-lateralized to all three deviants. To our knowledge there are no source-level studies on the late MMF to speech sounds. Therefore, a more accurate role of this response in speech or generally in sound processing remains to be determined with future studies employing speech and non-speech stimuli.

4.2. Group comparisons of MMF source strengths and latencies

We expected to find diminished MMF source amplitudes, less prominent lateralization to the left hemisphere, and delayed latencies in dyslexic than typical readers, but no significant group differences emerged. These results contradict with many previous studies, which have shown diminished MMNs to speech-sound changes in dyslexia or dyslexia risk (Schulte-Körne and Bruder, 2010, for a review). The only one previous study comparing MMFs in dyslexic and control participants to speech-sound changes (*/ba/* vs. */da/*) also failed to find group differences (Paul et al., 2006). The authors suggested that this could have resulted from a too large stimulus difference that was too easy to discriminate for their dyslexic children. This is consistent with previous observations showing diminished MMNs in dyslexia for small but not for large stimulus differences in tone frequency (Baldeweg et al., 1999). The same could be one reason for insignificant MMF source strength differences between the groups in our study.

Alternatively or additionally, the dyslexic subsamples of the different studies might differ in terms of their phonological deficits. An elaboration of the phonological deficit theory (Bradley and Bryant, 1983; Ramus, 2001; Ramus et al., 2013; Snowling, 2000) suggests that rather than the phonological representations per se, access to them may be impaired in dyslexia (Boets et al., 2013; Ramus and Szenkovits, 2008). The access of phonological representations is required for the Pig Latin and rapid naming subtests of the phonological processing composite, in which dyslexics of this study underperformed. This result combined with the present normal-like MMFs to speech-sound changes in our dyslexic group suggests that they had normal-like, but poorly accessible phonological representations. Future studies should determine the prevalence of core phonological deficits vs. dysfunctions in accessing or associating phonemes during reading in dyslexia in large participant samples. For instance, it was shown that dyslexics who displayed normal-like MMNs to phoneme changes presented with meaningless visual stimuli had diminished responses to the same changes when they were accompanied with written input (Mittag et al., 2013). Possibly, a larger proportion of dyslexics suffer from impairments in integrating and accessing of phonological information than merely from their poor representations.

In our previous study (Thiede et al., 2019) utilizing identical stimuli and paradigm as the current one, we found absent and atypical MMNs in infants at risk of dyslexia. This is quite a robust finding, since only ≈40–70% of children at risk of dyslexia become reading impaired (DeFries and Alarcón, 1996). The absence of such deficits in adult dyslexics suggests that neurobiological abnormalities in dyslexia might be more disruptive in infancy/childhood than in adulthood (see also, e.g., Lovio et al., 2010, reporting diminished MMNs to a range of speech stimuli in at-risk children). Possibly, speech development is originally delayed in dyslexia but speech processes become more normal by adulthood (Galaburda et al., 2006).

4.3. Correlation of MMF source strengths with reading-related skills

We also determined whether reading-related measures are associated with MMF source strengths. We found that larger MMF source amplitudes in the left hemisphere were associated with better working memory skills across both groups. *Post-hoc* analyses showed that the association was mainly driven by the MMF to the duration deviant and the verbal component of working memory. The result is in line with our hypothesis on positive correlations between MMF strengths and reading-related skills, and is consistent with previous studies that have shown associations between verbal working memory and MMN (Čeponienė et al., 1999; Watson et al., 2007) and late discriminative negativity (Hämäläinen et al., 2015), the equivalent of late MMN in children (LDN, Cheour et al., 2001). For example, children with increased verbal working memory performance had a larger MMN to consonant changes in speech sounds and tone frequency changes (Čeponienė et al., 1999; Watson et al., 2007). Yet, another study found no connection between the MMN and working memory in adults (Light et al., 2007). Compared to previous studies, our sample sizes are larger and we applied strict corrections for type I errors, which makes the findings more robust. The links others and we found between verbal working memory and neural speech discrimination suggest that accurate and efficient early stages of neural speech discrimination are paralleled by better verbal working memory performance. Working memory impairments especially in the phonological domain can delay or hamper language development in children (Adams and Gathercole, 2000). The phonological component of working memory has been linked with speech perception in noise. Working memory could solve mismatches, when noisy speech input and existing phonological representations are compared during speech processing (Millman and Mattys, 2017). This could also be a relevant mechanism during speech processing in everyday noisy conditions.

Even though this relationship between working memory and MMF source amplitudes was found across groups and in the control group, a separate analysis for the dyslexic group yielded no significant effects.

Possibly, the proposed connection between automatic speech processing and working memory could be disrupted in dyslexia, in which particularly verbal working memory problems are relatively common (Banai and Ahissar, 2004; Laasonen et al., 2009). Further investigations on the connections between working memory, reading, and speech processing are needed in order to better understand their role and interplay also in dyslexia.

An association was also found between the MMF strength and technical reading in the dyslexic group: consistent with our hypothesis, larger late MMFs were correlated with better reading skills. It is notable that the lack of this association in the control group could result from the lack of variation in the technical reading scores due to a ceiling effect (see Figure 1). The association of the late MMF to reading skills was similarly shown in children, i.e., increased left-hemispheric late MMN/LDN was associated with better word-reading skills (Maurer et al., 2009). The LDN has also shown associations to verbal working memory in children (Hämäläinen et al., 2015). The authors suggested that the LDN may reflect further processing of the speech-sound changes and/or attention-related processes relevant for reading. This could be the case also for the late MMF in the present study: it may reflect more complex neural processes than the MMF that may be more relevant for language and reading which has also been proposed in earlier studies (Hill et al., 2004; Korpilahti et al., 1995). The finding of correlations between late MMF and reading in our dyslexic group only emerging in the right hemisphere is novel. Other neurophysiological responses in the right hemisphere, such as enhanced ERPs to pseudowords and higher EEG correlation indices, have previously been associated with reading skills in dyslexic or reading impaired children (Byring et al., 2004; Lohvansuu et al., 2014). Our results might, therefore, suggest that some dyslexics have developed a right-hemispheric compensatory mechanism for speech processing that is also beneficial for their reading skills (Eden et al., 2004; Sebastian and Yasin, 2008).

4.4. Limitations

The following limitations of the present study should be considered. The first one relates to the selection of the study sample. Despite attempts to find matching groups of dyslexics and typical readers, typical readers still were more educated and had higher PIQ in our sample compared to the dyslexics. We addressed this by repeating our analysis with a performance-IQ -matched subsample and obtained similar results. Group sizes in this study were higher than in most previous studies, but still moderate consisting of 20+ participants in each group. Larger-scale studies should be carried out, as the neuroimaging field suffers from replication failures of previous results obtained with small sample sizes (Kellmeyer, 2017). As the expected effect sizes are generally small, many of these studies might be underpowered. Second, the stimuli chosen for the current study might not be sufficiently sensitive to reveal phonological deficits in adult dyslexics, since diminished MMNs have mostly been reported for consonant changes (Noordenbos et al., 2013; Schulte-Körne et al., 2001; Tuomainen, 2015).

The present study was not designed to compare speech- vs. non-speech processing and the influence of dyslexia on this processing, which has been a long-debated issue in the literature (see, e.g., Schulte-Körne and Bruder, 2010). Therefore, non-speech stimuli were not included in our experimental paradigm, and we cannot exclude the possibility that our findings also reflect basic auditory processes instead of, or in addition to, speech-specific processes. However, the left-hemispheric lateralization of MMFs in the present study is compatible with previous studies on speech processing, as pointed out earlier (Section 4.1).

4.5. Conclusions

To summarize, our results, advanced with source-localization constraints from individual anatomical brain images, support the suggestion of bilateral sources of the MMF to speech-sound changes in auditory cortices, as well as left-hemispheric lateralization of the MMF to vowel changes and well as late MMF to frequency, vowel, and vowel duration changes. We found comparable MMF strengths, latencies, and lateralization in typical and dyslexic readers, not supporting the proposed abnormalities in neural speech-sound discrimination in dyslexia. Possibly our stimuli were not sensitive enough to probe these deficiencies, or our participant subsample did not predominantly have phonological representation problems. However, we found correlations between the MMFs to speech-sound changes and reading-related skills, highlighting the connection of neural low-level speech processing and reading in adults, and promoting the use of MMFs in investigating reading-related brain processes.

Declarations

Author Contribution

A. Thiede: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

L. Parkkonen: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

P. Virtala, T. Kujala: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

M. Laasonen: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

J.P. Mäkelä: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This work was supported by Jane and Aatos Erkko Foundation, Academy of Finland [project numbers 2764141 and 316970], KELA (The Finnish Social Insurance Institution), and University of Helsinki MRI measurement support. Anja Thiede was supported by the University of Helsinki Research Foundation and Arvo and Lea Ylppö foundation.

Competing interest statement

The authors declare no conflict of interest.

Additional information

The clinical trial described in this paper was registered at ClinicalTrials.gov under the registration number NCT02622360.

Acknowledgements

The authors thank all participants that were involved in this study as well as all research assistants for their help with data acquisition and psychological testing, Marita Kattelus for her help with MRI acquisition, and the physician for examining the MRIs for incidental findings.

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NeuroImage 216 (2020) 116799

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Atypical MEG inter-subject correlation during listening to continuous natural speech in dyslexia

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ARTICLE INFO

Keywords:
Natural speech
Dyslexia
Inter-subject correlation
Magnetoencephalography
Reading skills

ABSTRACT

Listening to speech elicits brain activity time-locked to the speech sounds. This so-called neural entrainment to speech was found to be atypical in dyslexia, a reading impairment associated with neural speech processing deficits. We hypothesized that the brain responses of dyslexic vs. normal readers to real-life speech would be different, and thus the strength of inter-subject correlation (ISC) would differ from that of typical readers and be reflected in reading-related measures.

We recorded magnetoencephalograms (MEG) of 23 dyslexic and 21 typically-reading adults during listening to ~10 min of natural Finnish speech consisting of excerpts from radio news, a podcast, a self-recorded audiobook chapter and small talk. The amplitude envelopes of band-pass-filtered MEG source signals were correlated between subjects in a cortically-constrained source space in six frequency bands. The resulting ISCs of dyslexic and typical readers were compared with a permutation-based *t*-test. Neuropsychological measures of phonological processing, technical reading, and working memory were correlated with the ISCs utilizing the Mantel test.

During listening to speech, ISCs were mainly reduced in dyslexic compared to typical readers in delta (0.5–4 Hz) and high gamma (55–90 Hz) frequency bands. In the theta (4–8 Hz), beta (12–25 Hz), and low gamma (25–45 Hz) bands, dyslexics had enhanced ISCs to speech compared to controls. Furthermore, we found that ISCs across both groups were associated with phonological processing, technical reading, and working memory.

The atypical ISCs to natural speech in dyslexics supports the temporal sampling deficit theory of dyslexia. It also suggests over-synchronization to phoneme-rate information in speech, which could indicate more effort-demanding sampling of phonemes from speech in dyslexia. These irregularities in parsing speech are likely some of the complex neural factors contributing to dyslexia. The associations between neural coupling and reading-related skills further support this notion.

1. Introduction

Language processing and comprehension are essential for human communication and interaction. Neural speech processing deficiencies are typical for individuals with developmental dyslexia, a learning disorder characterized by reading and writing difficulties affecting up to 17% of the population (Elliott and Grigorenko, 2014). The speech processing deficit in dyslexia has been investigated widely (for reviews, see e.g. Ramus et al., 2003; Schulte-Körne and Bruder, 2010), however, mostly by utilizing unnatural, repetitive stimuli that barely resemble real-life speech. It has been argued that to truly understand the mechanisms of language processing in real-life situations, naturalistic stimuli should be used (Hasson et al., 2018). The core question of this study is whether the neural dynamics of processing natural speech are atypical in dyslexia.

This question has previously been illuminated from different angles. For example, acoustic and rhythmic properties of the speech stimulus *per se* are reflected in oscillatory brain activity, which has been suggested to enhance speech perception and comprehension (Doelling et al., 2014; Luo and Poeppel, 2007; Obleser and Weisz, 2012; Peelle and Davis, 2012), differently so in dyslexics than typical readers (De Vos et al., 2017a; Power et al., 2016). The natural brain rhythms (i.e., oscillations) thereby seem to interplay with the speech stimulus that is being processed (for a review, see Meyer, 2018). One interesting aspect, however,

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https://doi.org/10.1016/j.neuroimage.2020.116799
Received 20 June 2019; Received in revised form 21 February 2020; Accepted 30 March 2020
Available online 12 April 2020

has not gained much attention in the field of speech processing in dyslexia: Brain synchronization. When incoming information, such as speech, is processed in a similar manner across individuals, their neural activity is likely synchronized as well, which leads to a common understanding and goal-directed behaviour (Hasson et al., 2012). The extent of synchronization can be estimated with inter-subject correlation (ISC), a model-free analysis approach that has been proven viable to extract shared brain activations across participants during natural stimulation due to the time-varying dynamics of the stimulus (Hasson et al., 2004). ISC has been extensively applied during naturalistic paradigms in functional magnetic resonance imaging (fMRI), e.g. movie viewing (Hasson et al., 2004; Jääskeläinen et al., 2008; Kauppi et al., 2010; Nummenmaa et al., 2012), music listening (Abrams et al., 2013; Alluri et al., 2013), and speech processing (Wilson et al., 2008; Stephens et al., 2010; Lerner et al., 2011; Silbert et al., 2014; Finn et al., 2018). However, its application to magnetoencephalography (MEG) has been a lot scarcer. The only MEG ISC studies to date have looked at movie viewing with various ISC methodologies (Suppanen, 2014; Lankinen et al., 2014; Chang et al., 2015) and music listening (Thiede, 2014). The scarcity of MEG ISC studies could arise from the non-trivial methodology (e.g. complexity of the MEG signal, ill-posed source estimation problem), lack of ISC implementations for MEG as well as the substantial computational power required to do ISC analysis with MEG data. However, compared to fMRI, MEG can reveal new, complementary information that enables addressing slightly different questions. Whereas fMRI measures brain activity indirectly through the sluggish hemodynamic response and can only track fluctuations <1 Hz, MEG directly measures electric activity of neuronal populations with millisecond resolution. FMRI is also more affected by blood-oxygenating physiological processes in the body, e.g. pulsation and breathing.

The richness of the MEG signal allows extracting several measures (e.g. phase coupling, envelope correlation, cross-frequency coupling) across different frequency bands during rest or task. We focus here on one aspect; the envelope correlation in a set of frequency bands while the subject is listening to speech. ISC reflects functioning of cortical areas that respond to the time-varying stimulus dynamics, which in speech are manifold: For example, acoustic, phonological, syntactic, and semantic features likely activate lower- and higher-level brain functions related to processing and comprehension of speech. In fMRI studies, ISCs were found in healthy adult participants listening to natural speech in bilateral temporal areas, frontal areas, parietal areas including premotor cortex, and midline areas including precuneus (Wilson et al., 2008; Stephens et al., 2010; Lerner et al., 2011; Silbert et al., 2014; Finn et al., 2018). The first objective of the current study was to confirm and extend our knowledge of the brain areas that couple between healthy adult participants during listening to natural speech using MEG.

Certain brain dynamics have been repeatedly shown to be abnormal in dyslexia, specifically during speech processing. For example, temporal sampling deficits have been proposed to play a role in dyslexia, especially in the delta and theta band which reflect syllable encoding (Goswami, 2011; Hämäläinen et al., 2012; Molinaro et al., 2016). Moreover, Giraud and Poeppel (2012) have proposed that speech parsing at rates comparable to low-gamma frequencies is altered in dyslexia. Indeed, brain measures during processing of speech correlate with reading-related tests. For example, an abnormal right-rather than left-lateralized auditory steady-state response in dyslexics was associated with behavioural tests of phonology, and further, a phonemic oversampling, i.e. faster than normal oscillatory rate, has been associated with memory deficits in dyslexia (Lehongre et al., 2011). The second objective of the present study was to investigate whether brain activity of dyslexics during listening to speech is atypically synchronized compared to typical readers. We hypothesized that especially lower frequency bands (Goswami, 2011; Hämäläinen et al., 2012; Molinaro et al., 2016) show weaker ISCs between dyslexic than typical readers, whereas higher frequency bands could show enhanced ISCs between dyslexic compared to typical readers (Lehongre et al., 2011). Thirdly, we examined the association between ISC and neurophysiological measures across both groups. Previous research showed that behavior or trait characteristics were associated with ISC during listening to speech (Stephens et al., 2010; Finn et al., 2018). We hypothesized that the strength of ISC is associated with reading-related test performance.

These hypotheses were assessed by comparing the ISCs of MEG amplitude envelopes during listening to natural speech in dyslexic and typical readers. The MEG amplitude envelopes were extracted in the cortically-constrained source space of each individual in six frequency bands of interest (delta, theta, alpha, beta, low gamma, high gamma). Then, pairwise correlations were computed and averaged to obtain group correlations that were compared between groups. We found significant differences in ISC to speech between the groups, and could further show that the strength of ISC was associated with reading-related skills. These results reveal atypical processing of natural speech in dyslexia and show that these brain dynamics are reflected in reading-related skills.

2. Methods

This study has been preregistered at ClinicalTrials.gov (NCT02622360) as part of a research project on speech- and short-term memory functions in dyslexia.

2.1. Participants

Forty-nine Finnish-speaking right-handed adult participants aged 18–45 years and without a history of neurological diseases volunteered in the study, 26 with confirmed dyslexia and 23 typical readers. Participants were recruited from an organization for learning impairments (HERO Ry, Helsinki, Finland) as well as from university and adult education email lists, from a related project website, and by an advertisement in social media. To be included in the dyslexic group, participants had to have 1) a diagnosis from a psychologist, special education teacher, or similar, or 2) evident reading-related problems in childhood indicated by the adult reading history questionnaire (ARHQ; Lefly and Pennington, 2000) and confirmed in an interview, and 3) below-norm performance (less than one standard deviation from the age-matched average) in at least two reading subtests in either speed or accuracy (see Section 2.2). To be included in the control group, 1) participants or their relatives had to have no language-related disorders, 2) the ARHQ indicated no reading-related problems in childhood, and 3) participants had to perform within norm in at least two reading subtests. Exclusion criteria for the study were attention deficits (ADD) as tested by the Adult ADHD Self-Report Scale ASRS-v1.1 questionnaire (Kessler et al., 2005), other language impairments, such as developmental language disorder (formerly specific language impairment), other neurological or psychiatric diseases, medication severely affecting the central nervous system, a special education track in school indicative of wider cognitive impairments, non-compensated hearing or sight deficits, and a performance intelligence quotient (IQ) below 80. Data of four participants were excluded as anatomical MRIs could not be obtained due to metal in the body or pregnancy (three dyslexics, one control), and data from one participant had to be excluded due to technical reasons during the MEG measurement which resulted in missing trigger markers (control). The final sample consisted of 44 participants, of which 23 were in the dyslexic and 21 in the control group. Background information are summarized in Table 1; statistics were performed with SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Participants gave their written consent after they had been informed about the study. All procedures were carried out according to the Declaration of Helsinki, and the Coordinating Ethics Committee (Hospital District of Helsinki and Uusimaa) approved the study protocol.

2.2. Neuropsychological tests

Neuropsychological tests were conducted by Master students of psychology under the supervision of a licensed clinical psychologist in a

Table 1
Descriptive statistics about background information regarding both groups (dyslexic, control) and statistics for group differences. For scalar variables (age, education and musical education), means (M, bold) and standard deviations (STD) are reported and independent-sample *t*-tests are used for group difference statistics. For the categorical variable (gender), the count for each category (male/female, m/f) is reported and the X^2-test is used for group difference statistics.

Variable	Dyslexic group			Control group			Statistics		
	N	*M*	*STD*	*N*	*M*	*STD*	t/X^2	*df*	*p*
Age [years]	23	**31.6**	8.7	21	**30.0**	6.0	0.71	42	.482
Gender [count]	23	11/12	(m/f)	21	10/11	(m/f)	1.89E-04	1	.989
Education [years]	23	**15.7**	5.2	20	**17.0**	2.6	−0.95	41	.347
Musical Education [years]	23	**3.0**	7.8	21	**3.1**	4.8	−0.04	42	.972

session of ca. 2 h at the Cognitive Brain Research Unit, University of Helsinki. Domains of phonological processing, reading, IQ, and memory functions were assessed. Phonological processing was evaluated with the 'Pig Latin' test (Nevala et al., 2006), non-word span length (Laasonen et al., 2002), and rapid alternating stimulus naming (RAS; Wolf, 1986). Reading skills were evaluated by word and pseudoword list reading (technical reading) and text reading (Nevala et al., 2006). The verbal IQ was assessed with similarities and vocabulary subtests, and performance IQ with block design and matrix reasoning subtests (Wechsler, 2005). Memory function was evaluated with the subtests on number series and visual series (Wechsler, 2008). A summary of the neuropsychological test outcomes is presented in Table 2; statistics were performed with SPSS, effect sizes were calculated with Psychometrica Freeware (Lenhard and Lenhard, 2016), and bootstrapped confidence intervals were calculated with the measures-of-effect-size toolbox (Hentschke and Stüttgen, 2011, https://github.com/hhentschke/measures-of-effect-size-toolbox). Composite scores were formed for phonological processing and technical reading by converting the raw scores to *z*-scores and averaging them, and for working memory the composite was formed according to WMS-III (Wechsler, 2008).

2.3. Stimuli and data acquisition

Natural Finnish speech of ≈10 min was used as the auditory stimulus (sampling rate 44100 Hz; original sound file, transcription and its translation to English in Supplementary Material). The stimulus consisted of several shorter excerpts that were merged into one audio file with Audacity® 2.0 software (Audacity Team, http://audacityteam.org/). All excerpts were spoken by native Finnish speakers and either extracted from online sources (Finnish national broadcast 'Yle' radio news and podcast) or recorded by the experimenters (reading a book and small talk, such as asking for directions and exchanging of travel experiences) in a sound-proof laboratory at the Cognitive Brain Research Unit, University of Helsinki. The excerpts were chosen to represent a wide range of voices (male and female), topics, and style (conversation, factual, lyrical). Consecutive excerpts were joined with a 1-s silent break with 0.5-s fade-out and 0.5-s fade-in. The waveform of the speech stimulus is visualized in Fig. 1A.

The neural activity of the brain was recorded with an Elekta Neuromag Triux MEG system (MEGIN Oy, Helsinki, Finland) comprising 204 planar gradiometers and 102 magnetometers. The signals were filtered to 0.03–330 Hz and sampled at 1 kHz. Recordings were performed in a magnetically shielded room (Euroshield/ETS Lindgren Oy, Eura, Finland) at BioMag Laboratory in Helsinki University Hospital. Participants listened to the continuous auditory stream binaurally at a comfortable level (≈70–80 dB SPL). The stimulus was presented with Presentation Software (Neurobehavioral Systems Ltd., Berkeley, CA, USA) and conveyed from earphones to the ears via plastic tubes. Resting-state MEG data (eyes open) were recorded for each participant for ≈10 min. Other auditory and visual stimuli (written pseudowords and the corresponding auditory versions as well as scrambled visual symbols) had been presented before these recordings for ≈80 min in six recording blocks. Data from these recordings will be presented in separate publications. In all MEG recordings, participants were seated in an upright position and were instructed to relax and to listen to the continuous speech stimulus while keeping the head still.

Table 2
Descriptive statistics on neuropsychological test performances for both groups (dyslexic, control). Reported are means, standard deviations (in brackets), mean differences (*ΔM*) with bootstrapped confidence intervals (CI), *t*-values with degrees of freedom (*df*, in brackets) and *p*-values of group comparisons from independent-sample *t*-tests, and Cohen's *d* effect sizes for normally distributed scores in both groups. For non-normally distributed scores in one or both groups ($^{\#}$), median, interquartile range (in brackets), mean differences (*ΔM*) with bootstrapped confidence intervals (CI), *U*-values and *p*-values of group comparisons from Mann-Whitney *U*-tests, and Cohen's *d* effect sizes are reported. FDR-corrected significance levels are marked with asterisks (*p < 0.046, **p < 0.01, ***p < 0.001). Composite scores were formed for phonological processing and technical reading by converting the raw scores to *z*-scores and averaging them, and for working memory the composite was formed according to WMS-III (Wechsler, 2008).

Variable	Dyslexic group	Control group	Statistics			
			ΔM, CI	*t(df)/U*	*p*	*Cohen's d*
Phonological processing						
pig latin$^{\#}$	9 (7)	15 (1)	−4.59 [-6.61; −2.70]	77.00	***6.39E-05	1.434
nonword span length	11.26 (2.97)	13.00 (3.02)	−1.74 [-3.41; −0.01]	−1.92(42)	.061	−0.583
RAS time$^{\#}$	30 (11.5)	24 (6)	10.62 [6.37; 15.39]	64.00	***3.03E-05	1.617
Composite$^{\#}$	−0.20 (1.22)	0.49 (0.46)	−0.91 [-1.27; −0.56]	64.00	***3.04E-05	1.617
technical reading						
Word list Time$^{\#}$	31 (13.32)	19.28 (3.27)	15.08 [10.09; 21.14]	22.00	***2.50E-07	2.473
Word list accuracy$^{\#}$	30 (1)	30 (0)	−0.78 [-1.34; −0.34]	135.50	**.001	0.810
Pseudoword list time$^{\#}$	72.94 (37.27)	40.16 (9.33)	41.03 [28.12; 58.26]	5.00	***2.74E-08	3.068
Pseudoword list accuracy$^{\#}$	21 (9)	28 (4)	−7.63 [-10.13; −5.23]	40.50	***2.16E-06	2.028
Composite$^{\#}$	−0.34 (1)	0.61 (0.16)	−1.17 [-1.57; −0.84]	2.00	***1.83E-08	3.205
Working memory						
Composite	19.83 (4.80)	24.33 (4.95)	−4.51 [-7.30; −1.65]	−3.06(42)	**.004	−0.924
IQ						
verbal IQ	99.57 (13.26)	114.48 (7.43)	−14.91 [-21.37; −8.96]	−4.54(42)	***4.67E-05	−1.370
Performance IQ	109.67 (12.50)	121.17 (9.67)	−11.49 [-17.99; −5.21]	−3.39(42)	**.002	−1.023
Full IQ	104.62 (9.39)	117.82 (6.68)	−13.20 [-17.94; −8.64]	−5.33(42)	***3.68E-06	−1.609

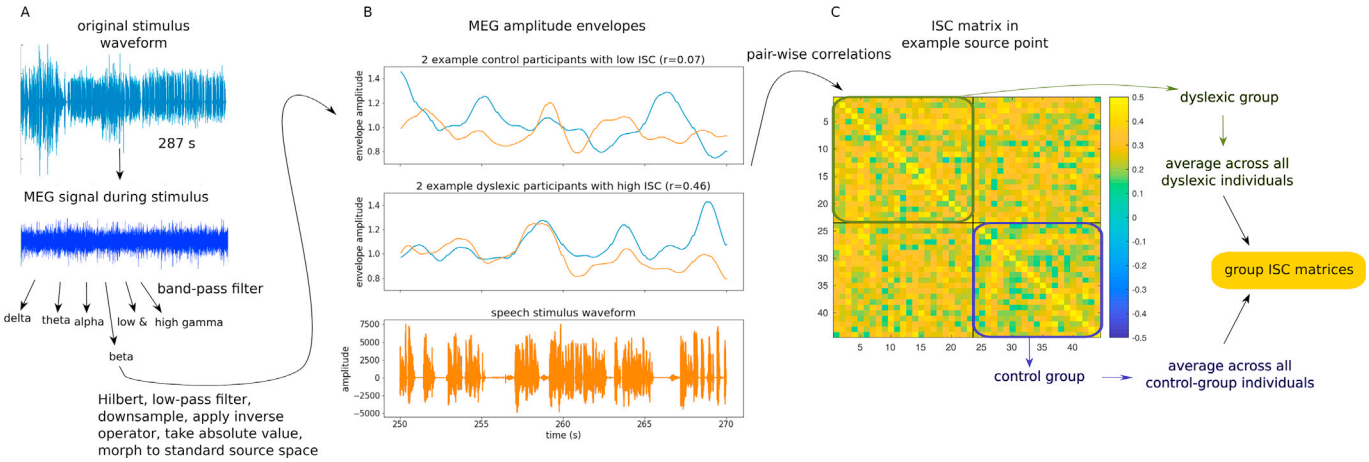

Fig. 1. Schematic representation of the inter-subject correlation (ISC) data analysis.
A. Acoustic waveform of the speech stimulus (part 1, duration 287 s). The MEG signal was extracted during the time of the stimulus. Here, the preprocessed MEG signal of an example channel (MEG1622) above the left temporal area is shown. The MEG signal was then filtered to six frequency bands (delta, theta, alpha, beta, low gamma, high gamma), Hilbert-transformed, low-pass filtered, downsampled, source modelled, and finally the absolute value was taken to obtain the instantaneous amplitude at every source point and in all six frequency bands. The source locations of these amplitude signals were then morphed from individual cortical source space to a standard source space.
B. Beta-band MEG amplitude envelopes of example participants showing low ISC (top panel) and high ISC (middle panel) at a source in the middle temporal cortex. The waveform of the speech stimulus during the same excerpt of 20 s is shown for comparison (bottom panel).
C. ISC matrix of all pairwise correlations at the same source location as in B). The upper left square (olive frame) contains ISC values for dyslexic pairs and the bottom right square (blue frame) for control pairs. Group ISC matrices were obtained at all source points by averaging across all individuals of one group.

In addition to MEG, scalp EEG and horizontal and vertical electro-oculograms (EOG) were recorded with a 60-channel cap (EasyCap, Herrsching, Germany) with reference and ground electrodes located at the nose and left cheek, respectively. Five head position indicator coils (HPI), the EEG electrodes, and fiducial markers of nasion and both pre-auricular points were digitized with a Polhemus Isotrak 3D-digitizer (Polhemus Inc., Colchester, VT, USA) in order to establish a transformation between the MEG and MRI coordinate systems. The HPI coils were continuously energized to enable tracking and compensation of head movements throughout the MEG measurement.

Structural T1-weighted magnetic resonance images (MPRAGE sequence) were obtained with a 3T MAGNETOM Skyra whole-body MRI scanner (Siemens Healthcare, Erlangen, Germany) with a standard 32-channel head coil at AMI centre, Aalto University. Each structural MRI consisted of 176 slices with a slice thickness of 1 mm, voxel size of (1 x 1 x 1) mm^3, and field of view of (256 x 256) mm^2. All structural MRIs were checked by a physician who reported no incidental findings.

2.4. Data analysis

The code used for the analysis of this dataset is available at https://github.com/athiede13/free_speech.

2.4.1. MEG data preprocessing

The continuous MEG data were preprocessed by first visually examining all recordings and marking noisy, flat, or otherwise artifact-containing channels as bad (on average 6.2 channels in one recording). External magnetic interference was suppressed with Maxfilter software version 2.2 (MEGIN Oy, Helsinki, Finland) applying temporal signal-space separation (tSSS; Taulu and Simola, 2006) with a buffer length of 10 s and correlation limit of 0.98. The algorithm also corrected for head movements measured with the HPI coils and interpolated the channels manually marked or automatically detected as bad. Physiological artifacts, specifically those resulting from eye blinks, eye movements, and heartbeats, were removed with signal-space projection (SSP; Tesche et al., 1995; Uusitalo and Ilmoniemi, 1997) implemented in MNE-Python (Gramfort et al., 2014, 2013) software package (version 0.17.dev0). Channels that showed the most prominent artifacts (EOG channels for eye-movements and channel 'MEG1541' for heartbeats) were used to average the artifact events and create the projectors. The noise covariance was estimated with MNE-Python from 'empty-room' data of ≈10 min that were preprocessed similarly to the data from the participants.

2.5. MRI data preprocessing

Structural MRIs were preprocessed using the Freesurfer software package (versions 5.3 and 6.0, Martinos Center for Biomedical Imaging, http://freesurfer.net/; Dale et al., 1999; Fischl et al., 1999a, 1999b). The steps applied included segmentation of brain volume with the watershed algorithm (Ségonne et al., 2004), intensity normalization (Sled et al., 1998), segmentation of grey and white matter (Fischl et al., 2004, 2002), and inflation of the cortical surfaces (Fischl et al., 1999a). Manual editing of surfaces, performed by an experienced graduate student, was required in 66% of the cases to ensure a correct segmentation of the brain volume and manual addition of white-matter points in 18% to ensure a correct segmentation of the grey and white matter boundary.

2.5.1. Coregistration

Coregistration of MRI and MEG was performed with the function *mne coreg* in the MNE-Python software package. First, the digitized fiducials and head-shape points (EEG electrode positions) were manually aligned with the reconstructed head surface from the individual anatomical MRI. Then, the iterative closest point algorithm was applied to minimize the distances of the head-shape points from the head surface.

2.5.2. Source modeling

The segmented cortical surface was decimated (recursively subdivided octahedron) to yield 4098 source points per hemisphere. A single-compartment boundary-element model (BEM) was applied to compute the forward solution; source points closer than 5 mm to the BEM surface were omitted. A dSPM minimum-norm estimate (MNE) inverse operator was then computed with a loose orientation constraint of 0.2, depth weighting exponent of 0.8, and the noise covariance estimated from the 'empty-room' data.

2.5.3. Inter-subject correlation (ISC)

For ISC computation (for an overview, see Fig. 1), custom scripts were utilized in MATLAB (release 2017a; The MathWorks, Inc., Natick, Massachusetts, USA) as well as the MNE Matlab toolbox (Gramfort et al., 2014) and MEG ISC custom functions (Suppanen, 2014; Thiede, 2014). First, in the listening-to-speech condition, the stimulus durations and temporal alignments with respect to the recordings were determined with the help of the stimulus start and end triggers from Presentation (due to technical reasons, the stimulus was in two parts; 4.77 and 5.45 min). For the determined stimulus durations, the preprocessed MEG signals were band-pass filtered (third-order Butterworth filter, applied in the forward direction only) into six frequency bands of interest (cut-off frequencies; delta: 0.5–4 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–25 Hz, low gamma: 25–45 Hz, high gamma: 55–90 Hz). The analytical signals were computed by applying Hilbert transformation to the band-pass-filtered signal. The resulting signals were low-pass filtered (similar filter as above) at 0.3 Hz, and downsampled to 10 Hz. The previously computed inverse operator was then applied to these complex-valued signals. The absolute value of each source time series was taken, resulting in cortical amplitude envelopes per each participant and frequency band (delta, theta, alpha, beta, low gamma, high gamma). The cortical locations of the envelopes were morphed from each individual subject to the Freesurfer standard brain (*fsaverage*) with MNE-Python. The source space of this standard brain consists of 20484 points per hemisphere, causing an automatic upsampling of the source points during the morphing step. Pairwise correlations of the cortical amplitude envelopes at the corresponding source points were computed across all subject pairs within each experiment group and for each frequency band. The pairwise correlations were averaged for each group, i.e., dyslexic and control group. A duration-weighted averaging was applied for the two speech parts.

To test whether ISCs were significantly larger than zero, a permutation-based one-sample *t*-test was applied to the group-average ISC matrices (MNE-Python function *spatio_temporal_cluster_1samp_test* based on Maris and Oostenveld, 2007). First, this test calculates the statistic (one-sample *T*-test) and forms initial clusters that are above the threshold using spatial neighborhood information; second, it permutes the data by randomized sign flips (subject pair labels are permuted here), finds clusters from each permutation, and returns the maximal cluster sizes; third, it returns clusters and corrected *p*-values that are computed as a percentile of the statistic within the 'null distribution' taken from the surrogate data generated by the permutations. The initial *p*-threshold for cluster formation was 0.05, the *t*-threshold was 1.97, and the number of permutations was 5000. The spatial connectivity was estimated from the *fsaverage* source space including all immediate neighbors. *T*-values of clusters that survived the cluster-*p*-threshold of 0.05/6 (Bonferroni--correction for the six frequency bands) were visualized.

The ISC contrast between the groups was then tested with a permutation-based *t*-test with 5000 permutations using custom-made Matlab and MNE-Python -based functions. First, surrogate difference maps were computed by randomly permuting subject labels for 5000 times and then calculating the independent-samples *T*-tests as recommended by Chen et al. (2016). Then, the independent-samples *T*-test was calculated for the unpermuted ISC data, and *p*-values were estimated for each source location (20484 locations). Cluster correction identified surrogate clusters consisting of spatially close source locations for each surrogate map (5000). The maximal cluster sizes were returned for each of the 5000 maps that represented the null distribution of cluster sizes. We then adopted the maximum statistics approach to control for all comparisons across all frequency bands (Winkler et al., 2016). From the surrogate maps obtained with permutations, the maximum of all maximal cluster sizes across all frequency bands (six bands) was computed as a cutoff for the real ISC contrast. Only clusters larger than the cutoff size were visualized on the *fsaverage* brain provided by Freesurfer.

2.5.4. Correlation between ISC strengths and neuropsychological tests

We tested for correlations between the brain-to-brain coupling strength during listening to speech (ISCs) and neuropsychological test scores using the Mantel test (Mantel, 1967). The neuropsychological test scores were combined into four composite measures: phonological processing, technical reading, working memory, and IQ (see Section 2.2).

Computations were carried out with custom scripts in MATLAB and MNE Python. Regression matrices were computed as models for the Mantel test by averaging the test scores between each subject pair for all four neuropsychological composites. Surrogate maps were computed by random permutation of the subject labels for 5000 times. The Mantel test was performed as a Spearman rank correlation between the top triangle of the ISC matrix (all pairwise combinations) and the top triangle of the regression matrix reflecting the neuropsychological composite (four composites of interest: phonological processing, technical reading, working memory, IQ). The ISC matrix contained values for each subject pair (946 pairs) and source location (20484 locations), and an uncorrected *p*-value was estimated for each source with the Mantel test. An uncorrected *r*-threshold was computed for each frequency band.

Cluster correction was performed by finding clusters for each surrogate map (5000) that exceeded the uncorrected *r*-threshold using the spatial connectivity information. For each model, the maximal cluster size was returned; the 5000 values represented the null distribution of cluster sizes. The maximum statistics approach was used also here, similarly to the analysis of the ISC group contrast. From the surrogate maps obtained with permutations, the maximum of all maximal cluster sizes across frequencies and neuropsychological composites (24 computations) was computed as a cutoff for the real Mantel data. Clusters were formed in the same way for the real Mantel data as for the surrogate maps, and only clusters larger than the cutoff size were visualized.

To showcase the distribution of correlation between each neuropsychological composite and ISC for control and dyslexic pairs, the Fisher-*z*-transformed mean ISC in the largest cluster was plotted against the corresponding composite scores for each frequency band.

3. Results

3.1. Interbrain correlation during listening to speech

ISCs were significantly larger than zero in all frequency bands and in both groups and exhibited different correlation strengths across frequency bands (Fig. 2, Table 3). Two large clusters encompassing the two complete hemispheres (with 10242 source locations in each) were found, because of the spatial spreading of the L2 MNE and the large number of sample pairs in the correlation computation.

There is an overlap of the ISCs of both groups in all frequency bands, only marginally in the theta band (Supplementary Figure 1). In the delta frequency band, the control participants had significant ISC in temporal, parietal, and central areas; the maximum was in the right midcingulate cortex (Table 3). Dyslexics exhibited ISC in right central and parietal areas, peaking at right postcentral areas. In the theta band, controls had synchronized activity in a defined area depicting the left anterior cingulate cortex, whereas in dyslexics the ISC pattern was more distributed towards left fronto–parietal and temporal areas, and right frontal and temporal areas, peaking at a location roughly corresponding to the left supplementary motor area. In the alpha band, ISC was found in bilateral inferior frontal gyrus, inferior temporal, and frontal areas with peaks in frontal areas in both groups. In the beta band, we observed bilateral frontal and temporal ISCs in both groups and the maxima were in left middle temporal cortex. The low gamma band showed frontal and parietal ISCs in both hemispheres in both groups, and additional strong bilateral occipital ISCs in the dyslexic group only. The high gamma band synchronized in both groups in bilateral superior parietal and postcentral areas that extended into occipital areas in the dyslexic group.

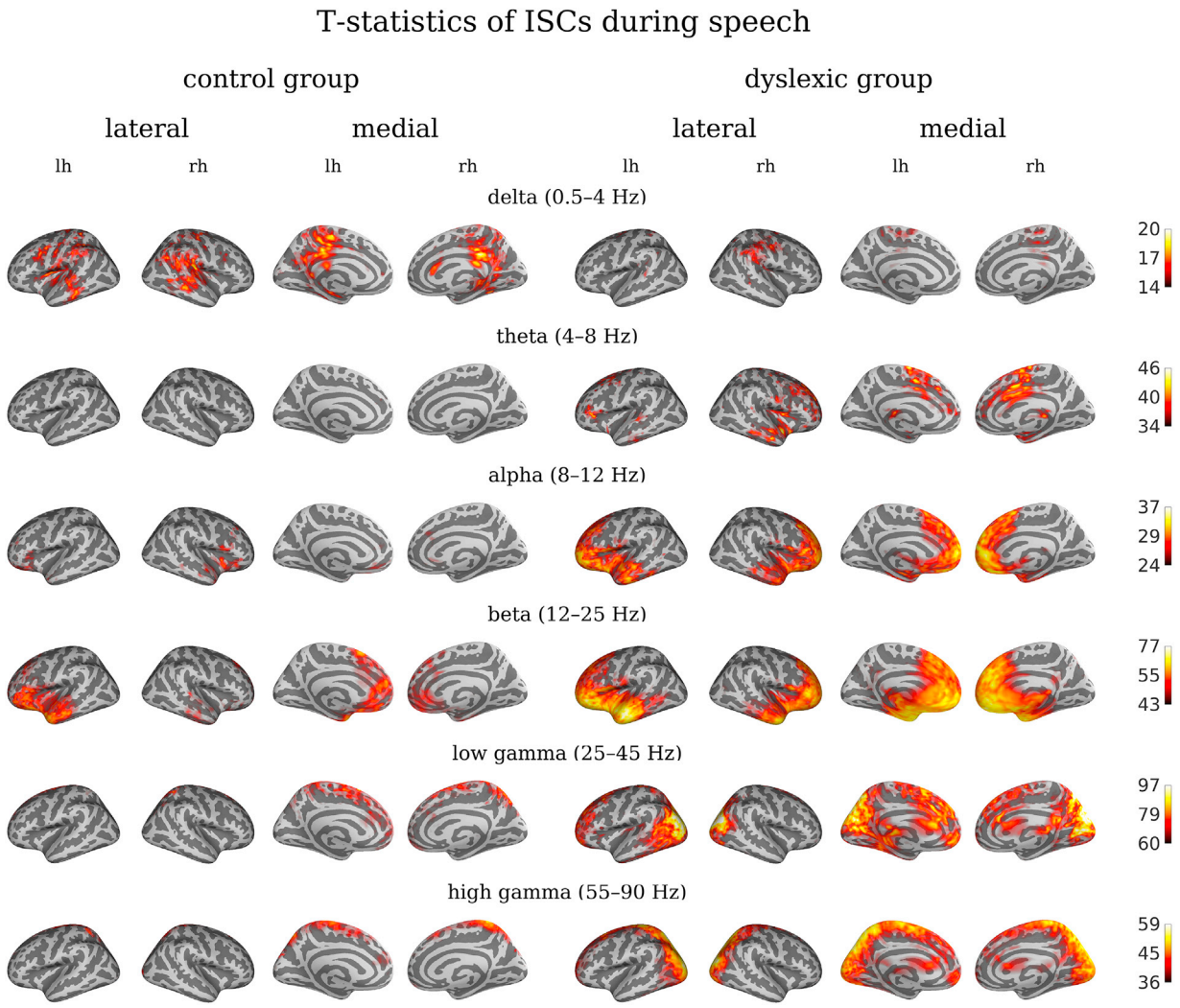

Fig. 2. *T*-statistics of permutation-based one-sample *t*-tests for inter-subject correlations (ISCs) during listening to speech in control (left four views) and dyslexic (right four views) group. ISCs are depicted in six MEG frequency bands (delta, theta, alpha, beta, low gamma, high gamma) in lateral (first two views of each group) and medial (last two views of each group) views (lh – left hemisphere, rh – right hemisphere). The lower *T*-value cutoffs were chosen as the 10th percentile of the data to highlight areas with highest ISC.

3.2. ISC differences between dyslexics and controls

Clusters depicting the brain areas that synchronized significantly differently between the control and dyslexic group are shown in Fig. 3, and the maximal differences of these areas are summarized in Table 3. Only clusters larger than 107 source points were considered significant as computed during the cluster correction. The results show that the ISC contrast between the groups manifested in distinct brain areas that differed between frequency bands. Whereas controls synchronized mainly stronger in the delta, and high gamma bands, dyslexics had stronger ISC in the theta, beta, and low gamma bands (Fig. 3).

In the delta band, typical readers had significantly stronger ISCs than dyslexics in bilateral auditory cortices, bilateral mid-cingulate cortices, and left central as well as frontal areas. In the theta band, a large cluster of stronger synchronization in the dyslexic than control group was found in the right middle and superior temporal, inferior and superior parietal, and central areas, peaking in the superior parietal cortex (Table 3). In the left hemisphere, stronger ISCs in dyslexics compared to controls were found in a superior parietal area. In the alpha band, no significant clusters were observed after corrections for multiple comparisons. In the beta band, stronger ISC was found in the dyslexic than control group in a left-hemispheric cluster including superior and middle temporal areas which also contained the maximal difference between the groups, as well as in more focal left-hemispheric occipital pole, superior parietal, and frontal areas. In the right hemisphere, dyslexics synchronized stronger than controls in superior and middle frontal areas including the frontal pole, as well as occipito–parietal areas. In the low gamma band, dyslexics showed stronger ISC in a large left-hemispheric cluster comprising occipital and temporal areas with a peak in the fusiform area as well as in a smaller cluster comprising occipital areas of the right hemisphere. In the high gamma band, controls had higher ISC than dyslexics in bilateral frontal, and right temporal areas, peaking in the right superior medial frontal cortex. In the same band, dyslexics had higher ISC than controls in a left occipital area.

3.3. Correlation of neuropsychological tests and ISC strengths

The regression matrices showing the mean values of neuropsychological test composites between each subject pair that were used as models for the Mantel test are visualized in Fig. 4. All significant correlations of neuropsychological composites and ISCs during listening to speech are visualized as clusters on the *fsaverage* brain in Figs. 5 and 6. Only clusters larger than 25 source points were considered significant. Alongside, the Fisher-*z*-transformed mean ISC in the largest cluster was plotted against the neuropsychological composite (for mean ISC vs. neuropsychological composite plots in the second-largest cluster, see Supplementary Figure 2).

Table 3
Peak MNI coordinates in significant frequency bands, cluster sizes, *t*/*r*-statistic (maximum/minimum of the largest cluster), and corresponding automated anatomical labeling (AAL) brain area (Brodmann area, BA, in brackets) for 1) ISC clusters during listening to speech for both groups, 2) ISC brain areas with group differences (con - control group, dys - dyslexic group), and 3) brain areas with significant regression between ISCs during listening to speech and reading-related measures.

frequency band	cluster size	MNI coordinates (x, y, z)			*t*/*r*	AAL brain area (BA)
1) ISC > 0						
CONTROL GROUP						
delta	10242	4	−31	30	20.57	Cingulum_Mid_R (23)
theta	10242	−11	39	23	36.80	Cingulum_Ant_L (9)
alpha	10242	−22	30	−11	30.83	Frontal_Inf_Orb_L (47)
beta	10242	−34	14	−34	65.48	Temporal_Pole_Mid_L (38)
low gamma	10242	12	−65	58	90.62	Precuneus_R (7)
high gamma	10242	12	−41	71	53.52	Postcentral_R (5)
DYSLEXIC GROUP						
delta	10242	40	−17	32	18.14	Postcentral_R (1)
theta	10242	−10	−7	65	45.78	Supp_Motor_Area_L (6)
alpha	10242	8	57	15	36.72	Frontal_Sup_Medial_R (10)
beta	10242	−50	−11	−21	76.89	Temporal_Mid_L (21)
low gamma	10242	18	−93	18	120.45	Occipital_Sup_R (18)
high gamma	10242	−15	−65	47	63.06	Parietal_Sup_L (7)
2) ISC(CON) vs. ISC(DYS)						
delta	5247	−27	−38	1	−6.97	Hippocampus_L (54)
theta	4523	24	−56	54	7.43	Parietal_Sup_R (7)
beta	4149	−50	−14	−18	9.02	Temporal_Mid_L (21)
low gamma	4474	−29	−70	−5	10.16	Fusiform_L (19)
high gamma	415	9	52	20	−5.46	Frontal_Sup_Medial_R (10)
3) CORRELATION OF ISCS WITH READING-RELATED MEASURES						
PHONOLOGICAL PROCESSING						
delta	6451	−57	−24	26	0.24	SupraMarginal_L (40)
theta	1047	41	−63	7	0.25	Temporal_Mid_R (19)
alpha	91	−8	−62	48	0.15	Precuneus_L (7)
beta	630	56	−15	40	0.29	Postcentral_R (1)
high gamma	71	−22	44	23	0.26	Frontal_Sup_L (10)
TECHNICAL READING						
delta	2395	−19	−51	2	0.18	Precuneus_L (30)
alpha	48	5	21	25	0.18	Cingulum_Ant_R (32)
low gamma	3695	−28	−70	−5	−0.28	Fusiform_L (19)
WORKING MEMORY						
delta	125	14	52	26	0.15	Frontal_Sup_R (9)
IQ						
delta	1331	−55	−23	28	0.23	Postcentral_L (1)

Significant correlations were found in all frequency bands, being predominantly positive (better reading-related skill was associated with higher ISC), except for technical reading in the low gamma band, where worse technical reading skills were associated with higher ISC in most brain areas. The brain areas of the peak correlations between neuropsychological composites and ISC are summarized in Table 3.

Phonological processing correlated with ISC during listening to speech in five frequency bands, i.e. all except low gamma (Fig. 5). The locations of significant correlations differed between the bands. The largest clusters were found in delta, theta and beta bands. In the delta band, significant correlations were found in left-hemispheric postcentral/superior parietal, precentral, supramarginal, frontal, transverse, middle and superior temporal areas as well as right-hemispheric central, frontal, inferior and middle temporal areas. The maximum correlation in the largest cluster between ISC strength and phonological processing scores was $r = 0.24$ in the left supramarginal gyrus (Table 3). In the theta band, significant clusters were found in left-hemispheric temporal pole, orbitofrontal, rostral middle frontal, and occipital areas. In the right hemisphere, the largest cluster was around the occipital pole extending into middle temporal areas where the peak was located. Other significant correlations were found at smaller inferior temporal and frontal-pole clusters in the right hemisphere. In the alpha band, bilateral superior parietal, and orbitofrontal areas were correlated with phonological processing, showing a maximum correlation at the left precuneus. In the beta band, left-hemispheric insula, and right-hemispheric middle and superior temporal, pre- and postcentral, pars opercularis, pars triangularis, caudal middle and rostral middle frontal areas showed significant correlations between phonological processing and ISC during listening to speech. The maximum correlation was $r = 0.29$ in the right postcentral area. In the high gamma band, small clusters in left superior frontal, and right superior parietal/postcentral areas were significantly correlated to phonological processing skills. The maximum correlation in the left superior frontal cluster was $r = 0.26$.

Technical reading correlated with ISC during listening to speech in the delta, alpha, and low gamma bands (Fig. 6). In the delta band, significant regressions between technical reading and ISC during listening to speech were found in the left superior and inferior parietal cortex, central, superior, middle and temporal areas, and insula. Right-hemispheric correlations were located in the inferior and middle temporal cortex, supramarginal, inferior parietal, and postcentral areas. The peak of the largest cluster was at the left precuneus. In the alpha band, bilateral anterior cingulate cortices showed significant correlations with technical reading. Whereas all other regressions indicated that better reading-related skills are associated with higher ISCs, in the low gamma band, also negative associations were found, indicating that worse technical reading was associated with higher ISCs. Negative clusters were found in left temporal and occipital areas, as well as orbitofrontal and superior parietal areas, the largest cluster having a peak at the left fusiform area. In the right hemisphere, occipital and inferior frontal, middle frontal and orbitofrontal areas were negatively associated with technical reading skills. Positive associations were found at a medium-sized cluster in the occipital right hemisphere. No significant regressions after corrections were found for the theta, beta, and high gamma band.

Working memory function correlated significantly with ISC in the delta band in a right superior medial frontal brain area (Fig. 6). In the other frequency bands, no significant regressions were found.

IQ correlated significantly with ISC in the delta band (Supplementary Figure 3). Left supramarginal, pre- and postcentral, insula, and medial

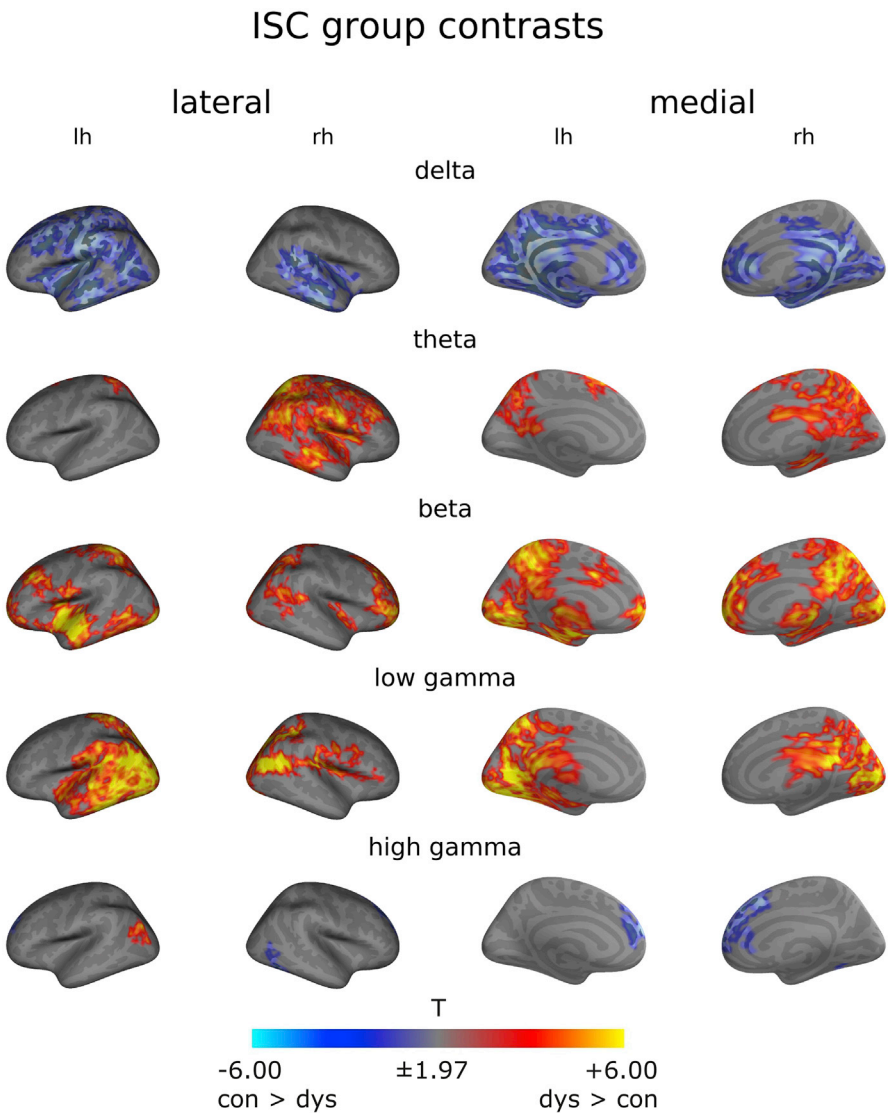

Fig. 3. Contrast of inter-subject correlations (ISCs) between the dyslexic and control group for listening to speech. Cold colors indicate stronger ISCs in the control than dyslexic group (con > dys), and warm colors stronger ISCs in the dyslexic than control group (dys > con).

temporal areas showed significant correlations, with the maximum in the left postcentral area. In the right hemisphere, ISCs in medial and inferior temporal areas, rostral middle and lateral orbitofrontal areas, as well as insula, were positively correlated with IQ. In the other frequency bands, no significant correlations emerged.

4. Discussion

The aim of the present study was to examine the neural dynamics of dyslexic and typical readers during listening to natural speech. To this end, typical readers and participants with confirmed dyslexia listened to several short excerpts of native Finnish speech while their neural activity was recorded with MEG, which – compared to fMRI – enabled us to analyze the temporal aspect of the neural signal in more detail. We found significant ISC in six commonly investigated frequency bands and could thus delineate neural dynamics at different paces, including the modulations of slow and fast rhythms in the brain. These rhythms are postulated to have neurophysiologically meaningful functions in speech processing (Meyer, 2018).

Firstly, our results confirm and extend the knowledge on between-subjects coupling of brain areas during listening to continuous speech. Secondly, our results suggest atypical ISC patterns during speech processing between dyslexic participants. We found lower ISC between dyslexic compared to typical readers in the delta, alpha, low gamma, and high gamma frequency bands, and mostly enhanced coupling between dyslexics in the beta band. Thirdly, reading-related measures were correlated with the strength of brain-to-brain coupling during listening to speech. The strongest correlations, observed in most of the frequency bands, were found for phonological processing, followed by technical reading, and working memory function.

4.1. Interbrain correlation during listening to speech

The ISC patterns we observed in typical readers were overall consistent with those previously found with fMRI during listening to natural speech (Wilson et al., 2008; Stephens et al., 2010; Lerner et al., 2011; Silbert et al., 2014; Finn et al., 2018). These fMRI studies and the results of the present study showed significant ISC in bilateral auditory cortices and language areas along the superior temporal cortex, parietal and midline areas, including precuneus, as well as frontal areas. The present results replicate earlier findings with complex natural stimuli, that is, consistent activation not only in primary sensory cortices but also in higher-order regions (Hasson et al., 2004; Lerner et al., 2011; Finn et al., 2018). Bilateral temporal areas are known to be involved in speech

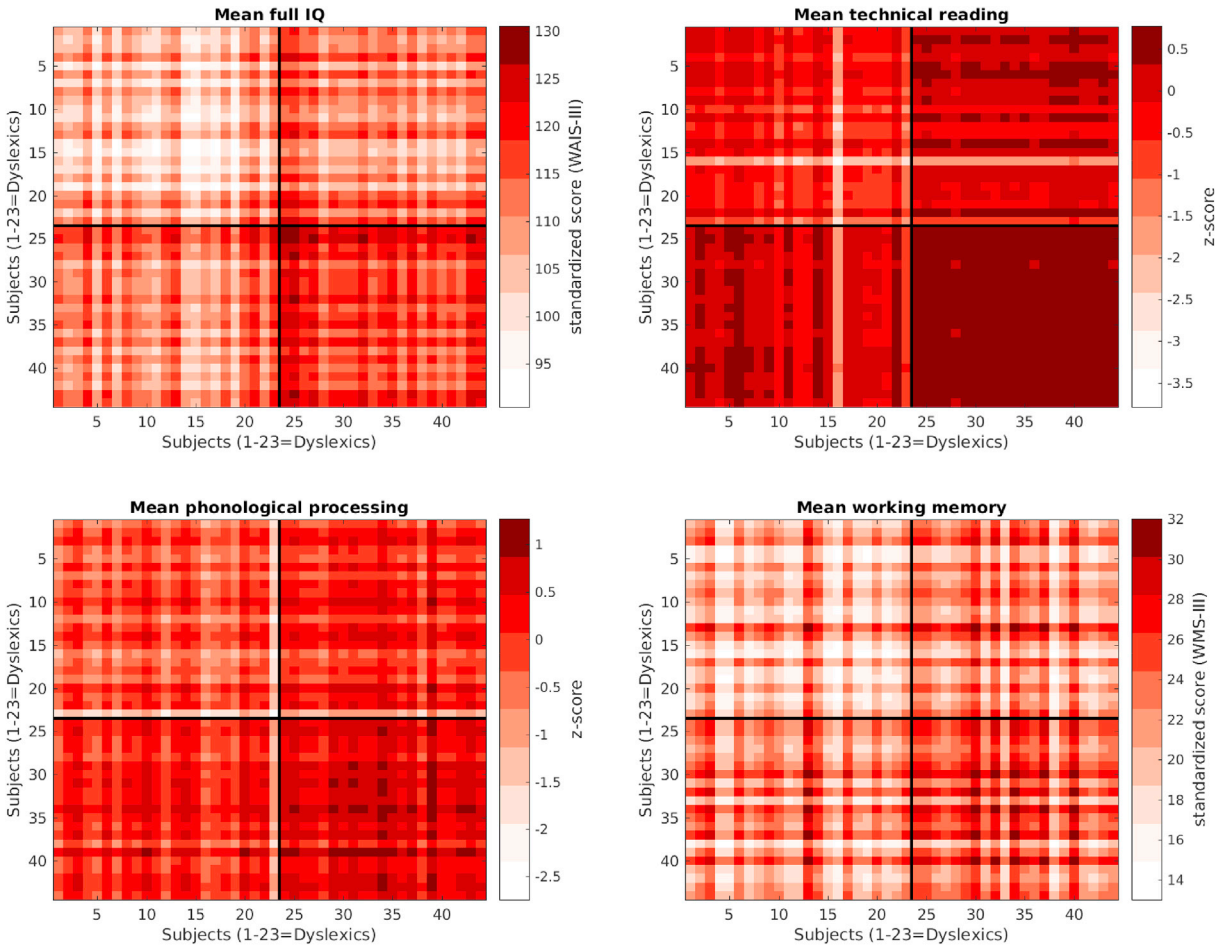

Fig. 4. Regression matrices for mean scores of neuropsychological test composites between subject pairs that were used as models for the Mantel test, which tested whether these behavioural models could be explained by the brain ISCs. *Z*-scores for phonological processing and technical reading. Standardized test scores for IQ and working memory.

processing and comprehension (see e.g., Hickok and Poeppel, 2007), and therefore were expected to show ISC in our study. In addition, other linguistically relevant and extralinguistic areas showed ISC during listening to speech. Of those, inferior frontal postcentral and parietal areas, specifically premotor areas, belong to a network involved in auditory and speech perception (Giraud and Poeppel, 2012; Schomers and Pulvermüller, 2016; Lima et al., 2016). Moreover, precuneus has been shown to play a role in higher-level social processes, such as role or perspective taking and episodic memory retrieval (Cavanna and Trimble, 2006), and it was suggested to be part of the theory-of-mind network together with STS and temporal-pole areas (Mar, 2011).

In addition, our dyslexic participants displayed ISC in occipital areas, for which previous fMRI studies have not reported ISC during listening to speech. Synchronized activity in occipital areas has recently been shown to support mental imagery and the elicitation of individual meanings of a narrative (Saalasti et al., 2019).

ISC in the beta band was maximal in the left temporal pole in the control group. Temporal pole has been previously associated to speech processing (Tzourio et al., 1998) as well as to semantic word processing or perception (Crinion et al., 2006; Marinkovic et al., 2003) and memory retrieval (Fink et al., 1996). Also the functional role of the beta band was suggested to be lexical–semantic prediction during speech comprehension (Lewis et al., 2015, 2016). Therefore, our results of maximal beta-band ISC in the left temporal pole could reflect processing of meanings of words in the continuous speech.

4.2. ISC differences between dyslexics and controls

To assess whether the extent of ISC differed between the dyslexic and control group, we compared the pairwise correlation maps between the two groups. We found that ISC was different between the groups in all frequency bands except alpha, however, with different patterns across the frequency bands. In the delta and high gamma bands, typical readers showed predominantly enhanced ISCs compared to dyslexic readers. On the other hand, ISC was stronger in dyslexic than typical readers in the theta, beta, and low gamma bands.

The enhanced ISC in the delta band in typical readers compared to dyslexics is consistent with the temporal sampling deficit theory (Goswami, 2011), which predicts that dyslexics especially in lower frequency bands would show a reduced sampling of information contained in the continuous speech stream. Delta-band synchronization is thought to be involved in the segmentation of intonation phrases (Giraud and Poeppel, 2012; Meyer, 2018). A reduced brain-to-brain coupling in this frequency band could therefore be indicative of deficits in temporally synchronized sampling of phrase boundaries. Previously shown reduced neural entrainment to the speech envelope in the delta band in dyslexics compared to typical readers (Molinaro et al., 2016) corroborates our results. Also phase locking to speech modulations at the delta rate was found to be atypical in dyslexia (Hämäläinen et al., 2012), suggesting additional delta-rate speech processing deficits.

Theta-band ISC was enhanced in dyslexic compared to typical readers in right parietal, frontal and temporal areas, being against our hypothesis

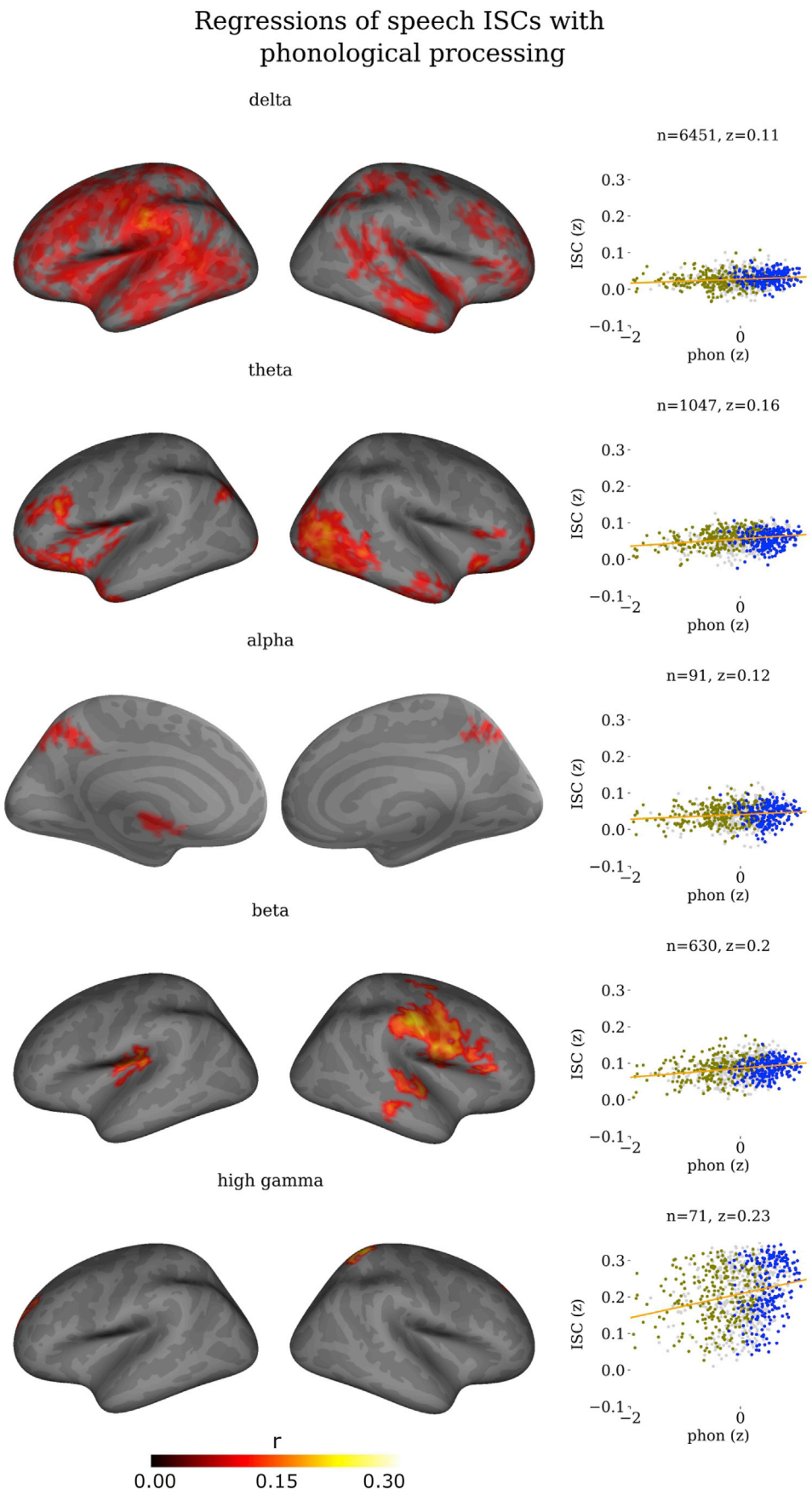

Fig. 5. Mantel regressions (*r*) between phonological processing and inter-subject correlation (ISC) adjusted with cluster correction. Left: Significant regressions on left and right brain hemispheres, lateral views, except for alpha band medial view. Right: Mean ISC (*z*) in largest cluster plotted against phonological processing score (*z*) for all subject pairs (ocre - dyslexic pairs, blue - control pairs, grey - mixed pairs) including a linear regression model (orange line). Cluster size (*n*) and the mean correlation in the largest cluster (*z*) are indicated above the scatter plots.

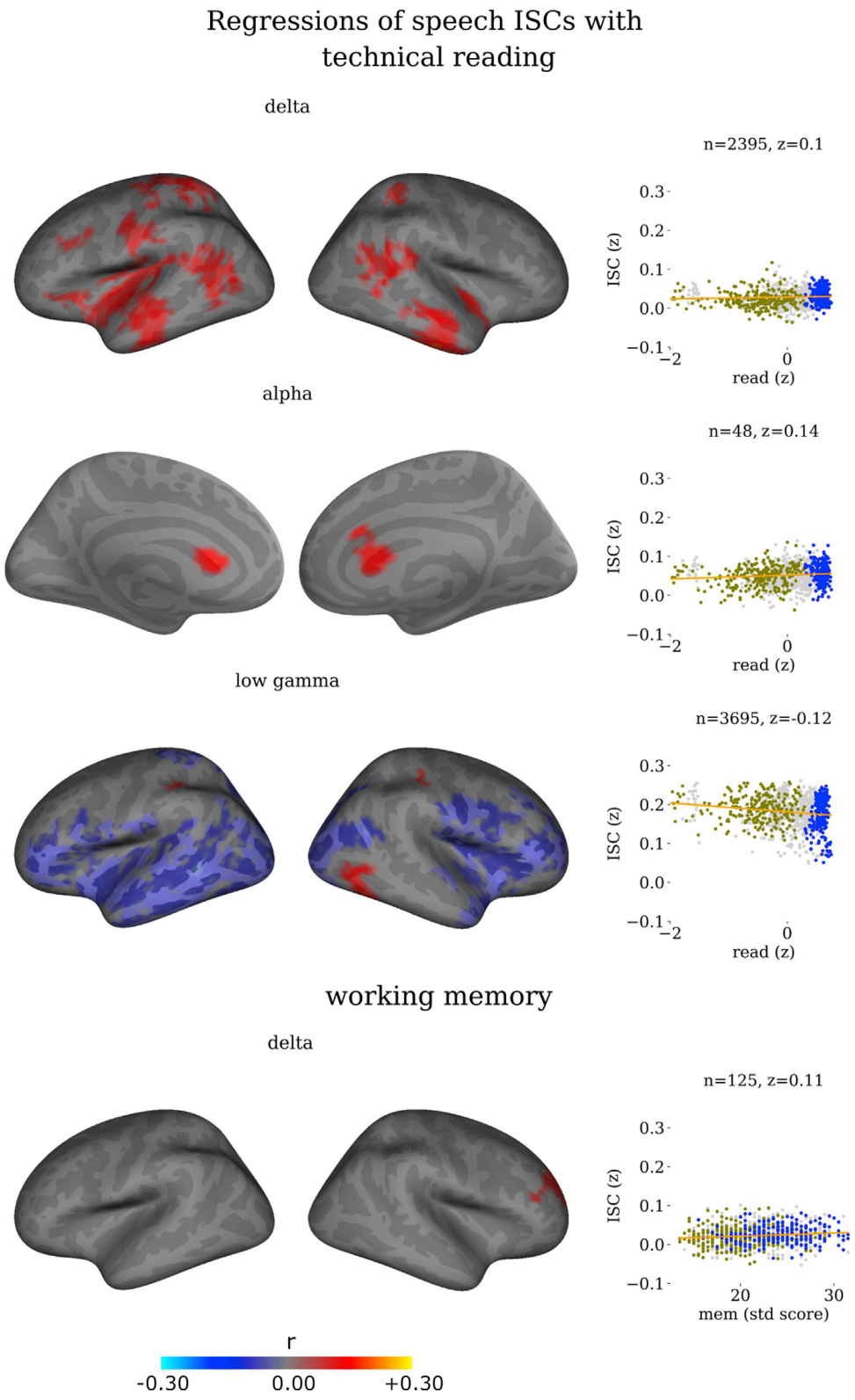

Fig. 6. Mantel regressions (*r*) between technical reading/working memory and inter-subject correlation (ISC) adjusted with cluster correction. Left: Significant regressions on left and right brain hemispheres, lateral views, except for alpha band medial view. Right: Mean ISC (*z*) in largest cluster plotted against reading score (*z*) or standardized working memory score for all subject pairs (ocre - dyslexic pairs, blue - control pairs, grey - mixed pairs) including a linear regression model (orange line). Cluster size (*n*) and the mean correlation in the largest cluster (*z*) are indicated above the scatter plots.

of reduced ISC in dyslexia (Goswami, 2011). The syllabic rate in speech lies within the theta range (Luo and Poeppel, 2007; Meyer, 2018). An oversynchronized brain activity in the theta band could therefore imply more effort-demanding parsing or oversampling of syllables in dyslexia. Our results are consistent with another study that reported enhanced synchronization (phase-locking values) in dyslexics compared to controls to 4-Hz rates which was interpreted as dyslexics needing to rely more on syllabic-rate information sampling than typical readers (Lizarazu et al., 2015).

The enhanced beta- and low-gamma-band ISCs in the dyslexics compared to controls support our hypothesis of enhanced coupling in higher frequency bands in dyslexia. Especially activity occurring in the gamma band is thought to track either phoneme-rate information or low-level acoustic features of incoming speech (Meyer, 2018). De Vos et al.

(2017b) showed that dyslexic children – when beginning to read – exhibited larger auditory steady-state responses to speech-weighted noise amplitude-modulated around 20 Hz (beta band), referred to as phoneme-rate modulations by the authors. This higher neural synchronization to phoneme-rate modulations was correlated with poorer reading and phonological skills in that study. Similarly trending results were obtained for dyslexic adolescents (De Vos et al., 2017a). In that light, our findings support the 'oversampling' hypothesis brought forward by Lehongre et al. (2011). According to this hypothesis, phoneme-rate information reflected in the beta and low gamma band could be oversampled, resulting in working-memory overload and therefore slower or less accurate extraction of phonemic information from speech. Alternatively, enhanced synchronization in the beta band has been suggested to be a compensatory mechanism for the processing of phonemic-rate information (De Vos et al., 2017a). The maximal ISC difference in the largest cluster between the groups was located in the left middle temporal cortex for the beta band and in the left fusiform areas for the low gamma band. In terms of phoneme processing, the left middle temporal cortex would be expected to play a major role, as it is an integral part of speech and word processing (Hickok and Poeppel, 2007). In fMRI studies, the peak location for differences between our groups found for the beta band has been frequently associated with activations during listening to speech in various ways (Narain et al., 2003; Oechslin et al., 2010; Straube et al., 2013; Nagels et al., 2013; Evans et al., 2016; Wolf et al., 2017).

In the high gamma band, the ISCs were weaker in bilateral frontal and right temporal areas and stronger in a left occipital area in dyslexic readers than in controls. The weaker ISC in dyslexics was rather unexpected, as we hypothesized that in higher frequency bands dyslexics could show higher ISCs than controls (Goswami, 2011; Lehongre et al., 2011). However, the role of the high gamma band in speech processing is still unclear (Meyer, 2018), even less so in dyslexia. The gamma band as a whole (usually $>$ 30 Hz) has been associated with numerous functions in speech processing, such as phonemic processing (Giraud and Poeppel, 2012), long-term memory processing (Ward, 2003), lexico–semantic retrieval (Pulvermüller et al., 1996; Mai et al., 2016) as well as tracking of phrase and syllable rhythms in continuous speech (Ding et al., 2015).

The natural stimulus presentation in the present study differs from the well-controlled designs often used in event-related neurophysiological studies. Despite the different paradigms, event-related brain responses are commonly filtered in the range from delta to beta or low gamma frequencies (i.e. around 0.5–30 Hz), and therefore the evoked-response-based findings on dyslexia (for reviews, see Hämäläinen et al., 2013; Kujala and Näätänen, 2001) may aid the interpretation of our ISC results. Sources of these responses during language-related tasks suggest functional differences between dyslexic and typical readers in left and right perisylvian language regions (for a review, see Heim and Keil, 2004). The results of the present study may reflect certain brain synchronization patterns that occur due to salient events in the continuous speech. As discussed in more detail above, these events may be related to different hierarchies of speech, such as phonemes, syllables, phrase boundaries etc.

Most of the above-mentioned studies that investigated oscillations during speech processing have looked at how brain signals in different frequency bands were following the speech signal. However, inter-subject synchronization during processing of speech has been studied to a much smaller extent. Our results show for the first time with MEG the synchronous neural processes between participants during speech processing, complementing earlier studies that investigated brain-to-stimulus coupling. The current approach focuses on how similarly speech was processed in the target groups, and how the synchronous neural processes differ between participants with or without dyslexia.

4.3. Correlation of neuropsychological tests and ISC strengths

ISC of both groups was significantly correlated with the neuropsychological composites of phonological processing, technical reading, and working memory. Correlations were found in most frequency bands for the phonological processing composite, followed by technical reading and working memory.

The phonological processing composite consisted of the 'Pig Latin' test, non-word span length, digit span length, and rapid alternating stimulus naming, all tapping into processing of phonological information. Large brain areas in delta, theta, and beta bands were positively correlated with phonological processing across both groups, meaning the stronger the brains synchronized, the better phonological skills the subjects had. A maximum correlation in the delta band was found in the supramarginal gyrus which incidentally was also the only area consistently correlated with IQ differences. The association between dyslexia and IQ has been a topic of debate for many years now (e.g. Shaywitz et al., 1995; for a review, see Stuebing et al., 2002). Following the recommendation of Dennis et al. (2009), we did not use IQ as a covariate, but rather investigated its association with ISC separately. In the theta band, the largest cluster indicating significant correlations could be located in the right middle temporal and occipital areas: higher ISC was associated with better phonological processing skills. Therefore, it could be that increased ISC in those areas reflects better speech parsing, thus leading to better phonological skills. In the beta band, the ISC in a large cluster around the right postcentral area was associated with phonological processing skills. According to the direct group comparison, this area was more strongly synchronized in typical than dyslexic readers, although in many other areas the opposite contrast was observed. It is possible that the phoneme information, the parsing of which is reflected in the beta band (De Vos et al., 2017b), was processed inefficiently by dyslexic readers in the postcentral right-hemispheric area and therefore the lower ISC was associated with worse phonological processing skills. In other words, typical readers with better phonological processing skills could be more efficient in processing phonemes reflected by higher ISC. Less entrainment to acoustic modulations around 30 Hz in dyslexics has also previously been associated with worse phonological processing, but better rapid naming skills (Lehongre et al., 2011). Due to the use of different subtests for phonological processing (the phonological processing composite in our study contained rapid naming as one of the subtests whereas Lehongre et al. (2011) separated phonological processing and rapid naming) and slightly different frequency limits (upper limit for the beta band was 25 Hz in our study) it is unclear whether their and our results tap on the same processes.

The technical reading composite comprised word and pseudoword list reading scores in speed and accuracy. Thus, this score merely reflects reading skills at the single-word level, but not, e.g., reading comprehension. Technical reading was positively associated to the ISC strength during listening to natural speech in the delta band, with the largest cluster at the left precuneus, a higher correlation between participants reflecting better technical reading scores. Although some of the brain areas that were correlated with technical reading overlap with those that correlated with IQ, the maxima differ. In line with the group differences in the delta band, a lower correlation between dyslexic participants is associated with worse technical reading skills. Low-level auditory processing could be related to the processing of phrase boundaries, corresponding to the delta-band frequencies (Giraud and Poeppel, 2012; Meyer, 2018). Abnormal low-level auditory processing can lead to impaired speech representations in the brain, which can affect reading abilities as in dyslexia (Bailey and Snowling, 2002; Goswami, 2015). In the low gamma band, the largest ISC cluster showed negative correlations with technical reading skills. Left temporal areas were included in this largest cluster, whereas right temporal areas did not show significant correlations, except in a small cluster of positive correlations. As the metric of technical reading skills is saturated in controls, it is possible that a higher ISC in left temporal areas in dyslexics reflects a compensatory mechanism for phoneme processing. This is also in line with the group comparison, as a higher ISC in dyslexics was observed in these areas, likely reflecting oversampling of phoneme information.

Working-memory capacity correlated with ISC strength only in the delta band. The correlation in such a low frequency band was rather

unexpected as Lehongre et al. (2011) previously associated a working-memory deficit with enhanced entrainment to rates above 40 Hz, i.e., in the higher gamma range. The right superior frontal area that was maximally correlated with working-memory capacity in the delta band did not appear to be significantly different between groups, although the direction of correlation suggests that a higher ISC would be associated with better working-memory skills, and these skills in our two groups are significantly different from each other. Associations with the delta-band have not been reported before and could be looked at in follow-up studies employing different methods. Possibly, a within-group correlation analysis could reveal further directions.

4.4. Limitations and future directions

The interpretation of ISC is the first limitation we want to address. First, for a certain brain region, ISCs in two frequency bands may also be explained by cross-frequency coupling (Canolty and Knight, 2010; Giraud and Poeppel, 2012). The ISC method used in this study is not adequate to disentangle cross-frequency coupling from independent synchronization in multiple frequency bands, and it should be investigated in *a-priori* defined bands and regions of interest, if applicable, with different methods, using both phase and amplitude information.

Future studies could investigate the effect of the age of the participants. Our participants were adults, and therefore the ones with dyslexia may have employed different compensation mechanisms and strategies for reading, which should be reflected as differences in those brain processes that are synchronized. A natural follow-up of this study would be to investigate these processes in children of different ages, i.e. before and after reading acquisition, to determine whether the atypical synchronization effects in dyslexia are rather due to genetic or environmental influences.

Another important point is the interpretation of cluster-based permutation tests. One should be aware that the results of these tests do not return a real spatial extent of the "significant" clusters (Sassenhagen and Draschkow, 2019). Therefore, the obtained shapes of the significant clusters are only observational. Despite those limitations, the cluster-based permutation tests are powerful in controlling for multiple comparisons in the high-dimensional MEG ISC matrices and were therefore the method of choice.

5. Summary and conclusions

With our novel approach of frequency-band-specific inter-subject correlation of MEG acquired during listening to natural speech, we showed that the strength of ISC differs between dyslexic and typical readers, with weaker ISCs in dyslexics in the delta and high gamma bands, and stronger ISC in dyslexics in the theta, beta and low gamma bands. Furthermore, the strength of ISC was associated with phonological skills as well as technical reading and working-memory function. Our findings shed light on how speech processing is reflected in different MEG frequency bands in healthy adults and in those with reading impairments and suggest how these brain dynamics are associated with behavioural outcomes. Unveiling speech processing in the brain in ecologically valid conditions can help uncover the complex neural basis of dyslexia.

Declaration of competing interest

None.

CRediT authorship contribution statement

A. Thiede: Conceptualization, Investigation, Formal analysis, Software, Data curation, Writing - original draft, Visualization, Project administration, Funding acquisition. **E. Glerean:** Methodology, Software, Formal analysis, Writing - review & editing. **T. Kujala:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition. **L. Parkkonen:** Resources, Formal analysis, Supervision, Writing - review & editing.

Acknowledgements

The authors thank all research assistants involved in the MEG and MRI recordings and neuropsychological testing. We would like to thank Emma Suppanen for providing us with the original version of the Matlab ISC scripts. Finally, we would like to thank all participants for their engagement in this study. This work was supported by Jane and Aatos Erkko Foundation and the Academy of Finland [project numbers 276414 and 316970]. The first author received funding from the Research Foundation of the University of Helsinki.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116799.

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IV

Brain structures associated with reading and their abnormalities in dyslexia: a whole-brain analysis

Running title: Neuroanatomy of dyslexia

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Abstract

Developmental dyslexia (DD) is a highly prevalent neurodevelopmental disorder, which often has a devastating influence on the individual's academic achievement and career. Research on the neural origins of DD has continued for half a century, yielding, however, inconsistent results. The current study was set out to determine abnormalities of grey and white matter volumes in adults with DD and to shed light on neural architectures associated with reading and related skills. To this end, we conducted a whole-brain voxel based morphometry following current recommendations on analysis approaches, coupled with rigorous neuropsychological testing, to characterize the associations between neuroanatomy and skills vital for reading in DD. We found decreased volumes of grey matter in DD, comprising a left-hemispheric network including superior temporal and inferior frontal gyri, insula, the limbic system, and basal ganglia, and white matter, including the right middle temporal gyrus and hippocampus, as well as the right precuneus. These results are both consistent with the most robust previous findings on cortical abnormalities in DD and yield novel insight to the role of subcortical structures in DD, scarcely studied so far. Crucially, areas with decreased grey matter in DD overlapped with brain areas associated with technical reading skills. This supports the conclusion that the grey matter regions that we identified to have a low volume in DD are associated with the core areas vital for reading.

Keywords: Developmental Dyslexia, Neuroanatomy, Voxel-based Morphometry, Grey Matter, White Matter

Declarations of interest: none

1. Introduction

Developmental dyslexia (DD) is a reading-skill impairment, which may emerge irrespective of adequate intelligence and reading instruction (Manual of Mental Disorders, 2000). The prevalence of dyslexia ranges between 5-17,5% (Shaywitz, 1998), which makes it the most common neurodevelopmental disorder. Due to its high prevalence and devastating influences on the individual's academic achievements, career, self-esteem, and coping in the modern society, it is pertinent to understand the neural basis of DD. Yet, this task is very challenging due to the heterogeneity of its geno- and phenotype (Kere et al., 2014; McArthur et al., 2013; Zoubrinetzky et al., 2014) and the complexity of the neural network underlying reading (Kujala et al., 2007).

According to functional imaging studies, the key neural network for reading comprises frontotemporoparietal circuits predominantly in the left hemisphere (e.g., Levy et al., 2009; Welcome and Joanisse, 2012). During word reading, the early visual processing occurs in the left inferior occipitotemporal (OT) cortex (Stoodley and Stein, 2013). The OT along with cerebellum are the starting points for the two major forward-driving nodes in the network of reading (Kujala et al., 2007). After the left OT areas, reading involves left parietal cortex and left inferior frontal gyrus (IFG; Levy et al., 2009).

The endeavor to find anomalies in the reading circuitry in DD to reveal its neural basis has continued for over 50 years (e.g., Drake, 1968; Ramus et al., 2018). However, the previous morphological studies, including those utilizing modern neuroimaging methods, have offered relatively few replicated results on the neural basis of DD and the association between neuroanatomy and skills pertinent for reading.

The current study employed a rigorous neuropsychological testing of cognitive functions vital for reading and voxel-based morphometry (VBM), an automated MRI method for assessing focal brain changes (Ashburner and Friston, 2000). Since its introduction, VBM has become a standard method to analyze neuroanatomical abnormalities in various disorders, including DD with over 20 published studies (Brambati et al., 2004, Brown et al., 2001, Dole et al., 2013, Eckert et al., 2016, Eckert et al., 2005, Evans et al., 2014, Hoeft et al., 2007, Jednoróg et al., 2015, Jednoróg et al., 2014, Krafnick et al., 2014, Kronbichler et al., 2008, Menghini et al., 2008, Pernet et al., 2009a, Pernet et al., 2009b, Silani et al., 2005, Siok et al., 2008, Steinbrink et al., 2008, Tamboer et al., 2015, Vinckenbosch et al., 2005, Xia et al., 2016, Yang et al., 2016). Whereas the results have been spatially discorded in DD, the most frequently reported brain regions in VBM findings include left posterior temporal and temporoparietal areas, but with both increased and decreased grey matter (GM) volume reported in DD (e.g., Brambati et al., 2004; Silani et al., 2005; Hoeft et al., 2007). In addition, DD has been associated with reduced GM (both modulated and non-modulated data) bilaterally in the frontal lobe (Brown et al., 2001) as well as in the left superior frontal gyrus and IFG (Brown et al., 2001; Brambati et al., 2004), bilateral OT regions (Brambati et al., 2004; Eckert et al., 2005; Kronbichler et al., 2008), subcortical structures (caudate and thalamus, Brown et al., 2001), and cerebellum (Brown et al., 2001; Brambati et al., 2004; Eckert et al., 2005; Kronbichler et al., 2008). However, a number of studies with no significant morphological findings in DD have also been published (e.g., Pernet et al., 2009a, b; Casper et al., 2018).

Reduced WM volumes in DD have been reported in left-hemispheric frontal areas, post-central gyrus, paracentral lobule, and temporo-parietal region (Eckert et al., 2005; Silani et al., 2005). Furthermore, WM volume reductions have been reported subcortically, in striatum and

hippocampus (Wang et al., 2019), and with a matched-brain morphometry approach, in corona radiata, internal capsule (Eckert et al., 2017).

Three recent meta-analyses have tackled with the heterogeneous morphometric findings in DD. In 2013, Richlan and colleagues evaluated nine VBM studies on DD and found reduced GM in the superior temporal areas bilaterally in DD (Richlan et al., 2013). A few years later, Eckert and colleagues evaluated 11 VBM studies on DD, and reported lower GM volume (i.e. modulated data; adjusted for total GM volume) in left superior temporal sulcus, left orbitofrontal cortex, and the right cerebellum in participants with DD (Eckert et al., 2016). Interestingly, one of the most robust findings is reduced total brain volume in subjects with DD compared with typical readers, a finding confirmed by a meta-analysis including 1164 participants across 18 studies (Ramus et al., 2018). However, the direction of association between the reduced brain volume and DD, let alone its possible aetiological factor for DD remain currently unknown.

Overall, there is enormous variation between the results obtained on the structural brain anomalies in DD, which presumably partly results from the heterogeneity of DD, but also has raised the concern of their reliability (Ramus et al., 2018). Across the published studies, a mixed selection of statistical thresholding and corrections for multiple tests have been applied, if any. When voxel-based neuroimaging methods (e.g. VBM) are used to reliably identify the neuroanatomical changes in DD, a combination of reasonable cluster-size threshold and voxel extent is needed to produce a desirable balance between Types I and II error rates (Lieberman and Cunningham, 2009). In addition, most of the studies consist of small sample sizes, with only few studies including more than 16 dyslexics (see Eckert et al., 2016, for a meta-analysis). Furthermore, consistency in adjusting the morphological analyses for confounding effects is

lacking. Another core problem is the bias for publishing studies reporting group differences. Due to these reasons, diving the more robust findings from the less reliable is challenging (see Ramus et al., 2018, for a review).

To attain reliable VBM results, it is critical how the preprocessing of MRI data is carried out, in other words, how the GM and WM probabilistic maps are formed. As in any voxel-based imaging analysis, following published guidelines, ensuring efficient registration, as well as controlling for factors that affect brain size (e.g. age) aid to achieve dependable results and extra sensitivity (Barnes et al., 2010; Ashburner and Friston, 2001; Pell et al., 2008; Li X et al., 2013; Da Ma et al., 2018). One crucial preprocessing step is modulation, which allows testing for regional differences in the absolute amounts (volume) of GM or WM (Ashburner and Friston, 2000; Good et al., 2001). Ramus et al. (2018) published a well-founded list of methodological recommendations for more reliable research on the neuroanatomy of DD and encouraged to systematically use relevant covariates to diminish their confounding effects on between-subject comparisons. In general, it is strongly recommended to include an adjustment for head size and other nuisance variables like gender and age in the morphological analyses (Barnes et al., 2010; Da Ma et al., 2018; Li X et al., 2013; Pell et al., 2008). Moreover, other seldom controlled variables in DD analyses are verbal and full-scale intelligence quotients (IQ), which were suggested to be correlated with brain size (McDaniel, 2005).

Based on this information, and following the previously published recommendations (Ramus et al., 2018), we set out to evaluate the GM and WM volume abnormalities in adult dyslexic individuals, whose reading-skill and neuropsychological profiles were rigorously assessed with a carefully composed test battery. We investigated brain properties while systematically using relevant covariates in the analyses. Furthermore, the connection between regional GM and WM

volume and reading-related skills were analyzed as well as the association between these skills and group findings.

2. Materials and methods

2.1 Procedure

The data were collected in three separate sessions. In the first session neuropsychological testing was carried out. The second session included functional imaging (combined magneto- and electroencephalography, the data from which will be reported elsewhere) and responding to questionnaires. In the third session, anatomical MRI data were acquired.

2.2 Participants

Participants were recruited via social media, website of a related project, and through a local learning disabilities association. Forty-five right-handed Finnish-speaking participants completed the MR-imaging, the final sample consisting of 22 typically reading and 23 dyslexic participants. The groups were balanced in age, years of education, years of music education (since it may improve language skills; see, e.g., Kraus and Chandrasekaran, 2010), and sex (see Table 1 for descriptive statistics). The groups showed no significant differences in the demographic variables, whereas they significantly differed in the composite scores of phonological processing, technical reading, and working memory (Table 1). However, they differed in the full-scale IQ (FIQ), which was, therefore, used as a covariate in the analyses.

The participant was classified as dyslexic if 1) a recent statement on dyslexia diagnosis was available from a health-care professional (e.g., psychologist), or the participant had both 2) reading-related problems in childhood as evaluated with the adult ARHQ and confirmed in an interview, and 3) a performance of at least one standard deviation (SD) below the average of age-matched standardized control data (Laasonen et al., 2010) in at least two different reading

subtests (word list reading, pseudoword list reading, text reading) in either speed or accuracy (Table 1). Participants classified to the Control group 1) had no language-related problems (and neither did their parents nor siblings), 2) reported no childhood problems in reading or writing as indicated by the ARHQ, and 3) performed within norm in at least two reading subtests in both speed and accuracy.

Please, insert Table 1 around here

The exclusion criteria were as follows (self-reported except for IQ, which was tested): attention deficit evaluated by the Adult ADHD Self-Report Scale ASRS-v1.1 questionnaire (Kessler et al., 2005), developmental language disorder or other language impairments, other neurological or psychiatric disorders, substance abuse, medication affecting central nervous system, uncorrected hearing or visual deficit, left-handedness, an individualized school curriculum, early bilingualism, and a performance IQ below 80. MRI data of four participants could not be obtained due to non-detachable metal in the body or pregnancy (three dyslexics, one control).

The experiments were undertaken with the understanding and written consent of each subject, and following the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa approved the study protocol.

2.3 Neuropsychological tests and questionnaires

Participants filled out questionnaires concerning background information, DD in family, Adult Reading History Questionnaire (ARHQ; Lefly & Pennington, 2000), and Attention-Deficit/Hyperactivity Disorder (ADHD) Self-Report Scale Symptom Checklist ASRS-v1.1 (Kessler et al., 2005). The questions on the background included the participants' language

skills and usage; language difficulties, neurological, psychiatric, and hearing disorders of him/her and the relatives (parents and siblings); the participant's other health issues and vision; music education and listening; and education and employment status. One questionnaire assessed the family history of DD.

The neuropsychological test battery was designed to assess IQ, reading, phonological processing (phonological awareness, phonological short-term memory and rapid access of phonological information; Torgesen et al., 1994), and working memory functions (Table 2). The verbal IQ was evaluated with the subtests Similarities and Vocabulary, and the performance IQ was assessed with the subtests Block Design and Matrix Reasoning from the Wechsler Adult Intelligence Scale III (Wechsler, 2005). Technical reading skills (accuracy and speed, Cronbach's α = .87) were tested with word and pseudoword list reading (Nevala et al., 2006). The domain of phonological processing (Cronbach's α = .69) included neuropsychological tests as follows: 'Pig Latin' test for assessing phonological awareness (Nevala et al., 2006; the participant is asked to change the first syllables between two heard pseudowords and produce aloud the new pseudowords, e.g., kouta-mesi -> meuta kosi), non-word span length for phonological short-term memory (Laasonen et al., 2002; the participant repeats lengthening sequences of heard pseudowords, e.g., pola-sine-heka), and rapid alternating stimulus naming for rapid serial naming (Wolf, 1986; the participant names as rapidly and accurately as possible a 10x5 matrix of alternating colors, letters, and numbers). Working memory functions were evaluated with Letter-number Series and Visual series subtests from the Wechsler Memory Scale, WMS-III (Wechsler, 2008).

We chose to use composite scores instead of the individual variables of single tasks for two reasons: in order to reduce the number of analyses and to reduce the error variance related to single task performance. Unfortunately, the size of the data in the current study did not allow for conducting a factor analysis over the variables and, thus, were chose to use the

classifications based on previous theoretical and factor-analytic studies but also checked the internal consistency of our domain variables with Cronbach's α (see above). Composite scores of the test results (bolded in Table 2) were formed for phonological processing and technical reading by converting the raw scores (of subtests listed in Table 2 below the respective composite) to *z*-scores and averaging them, and for working memory the composite was formed according to WMS-III (Wechsler, 2008).

Please, insert Table 2 around here

2.4 MRI data acquisition

Participants were scanned with a 3T MRI Siemens Skyra scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil, at AMI center in Aalto University, Finland. High-resolution magnetization prepared rapid acquisition gradient-recalled (MPRAGE) T1 images were obtained (flip angle = 7°, TR = 2530 ms, TE = 3.3 ms, voxel size = 1.0 x 1.0 x 1.0 mm^3).

2.5 Data analysis

2.5.1 Voxel-based morphometry

Morphometric analysis was carried out using VBM (Ashburner and Friston, 2000) and the Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, UCL) under MATLAB 8.0.0 (The MathWorks Inc., Natick, MA, USA, version R2014b). VBM is an MRI analysis technique that allows comparison of GM and WM differences in focal brain regions between groups (Ashburner and Friston, 2000). After

reorienting the individual T1 images using the anterior commissure as a landmark for the origin, Unified Segmentation (Ashburner and Friston, 2005) with medium regularization was applied to the T1 images, segmenting them precisely into GM, WM, and cerebrospinal fluid probability maps before normalizing them into the Montreal Neurological Institute (MNI) space using SPM8 normalization. To preserve the original signal strength during the normalization, GM and WM probability maps were modulated. After this, to reduce residual inter-individual variability, GM and WM probability maps were smoothed using an isotropic spatial filter (FWHM = 6 mm). During each step, the images were visually checked for potential registration errors. Modulated probability maps were used to calculate TIV (volumes of GM, white matter volume and cerebrospinal fluid added together), TBV (GM volume and white matter volumes added together) (Malone et al., 2015).

2.5.2 Statistical analyses

Preprocessed GM and WM images were then entered into a second-level analysis. First, three one-sample t-tests including all subjects (N=45) were calculated to evaluate the focal GM and WM structures associated with better performance in technical reading, phonological, and working memory tests. Then, using independent-sample t-tests, two different contrasts (Controls>Dyslexics, Dyslexics>Controls) were calculated to evaluate the GM and WM volumetric differences between the dyslexics and controls. All results were corrected for nonstationarity (Hayasaka et al., 2004) and spmT-maps were thresholded at a whole-brain uncorrected P<.005 threshold and a familywise error rate (FWE) corrected P<.05 at the cluster level, a combination which has been shown to produce a desirable balance between Types I and II error rates, comparable to false discovery rate (FDR)(Lieberman and Cunningham, 2009), and corrected for non-isotropic smoothness using VBM8 toolbox (http://dbm.neuro.uni-

jena.de/vbm8/VBM8-Manual.pdf). Exact neuroanatomical regions were identified using the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002) included in the xjView toolbox (http://www.alivelearn.net/xjview/).

Partial correlations (two-tailed) were calculated between each individual significant cluster and the three composite scores (technical reading, phonological processing, working memory; see Table 1) using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). To control for multiple comparisons, FDR approach was used and only significant results are reported.

All statistical analyses were adjusted for age, gender, and TIV (Barnes et al., 2010; Da Ma et al., 2018; Li X et al., 2013; Pell et al., 2008). Furthermore, to follow the previously published recommendations (Ramus et al., 2018) and to take into account the group difference, FIQ was also added as a covariate.

3. Results

3.1 Anatomical correlates of neuropsychological tests

We first determined how reading, phonological processing, and working memory were associated with brain structures including both groups in the analysis (Fig. 1; Table 3). Better performance in technical reading (accuracy and speed combined) was associated with greater GM volume in a cluster comprising the left temporal (STG and middle temporal gyrus (MTG), fusiform gyrus), limbic (amygdala, hippocampus, parahippocampal gyrus) and insular areas ($R=.634$, $P<.001$). In addition, better technical reading performance was associated with greater WM volume in one cluster comprising right frontal areas (IFG and precentral gyrus), basal ganglia (putamen, globus pallidus), insula, pons, parahippocampal gyrus, and left cerebellum ($R=.606$, $P<.001$). Higher working memory scores were associated with greater WM volume in the brainstem and bilaterally in the cerebellum ($R=.518$, $P=.001$).

When the two significant WM clusters (i.e. technical reading and working memory) were overlaid with white matter atlas (https://www.natbrainlab.co.uk/atlas-maps) for visualization purposes, both bore a resemblance to cortico-ponto-cerebellar (CPC) tracts (Fig. 1). We carried out an exploratory *post-hoc* analysis evaluating the amount of overlap between the two WM clusters and the CPC tracts. From technical reading WM cluster, 24.4% situated in the right CPC and from the working memory WM cluster, 23.7% and 33.5% situated in the left and right CPC pathway, respectively.

Please, insert Fig. 1 around here

Please, insert Table 3 around here

3.2 Neuroanatomical group differences

First, we evaluated whether the controls and dyslexics had significant brain volumetric differences in TIV, total brain volume, GM, WM or cerebrospinal fluid. Five independent-sample *t*-tests were performed, out of which none were statistically significant. The groups showed no significant differences in TIV t(43)=.083, P=.934, total brain volume t(43)=.434, P=.666, GM volume t(43)=.381, P=.705, WM volume t(43)=.415, P=.680 and cerebrospinal fluid t(43)=-.232, P=.817.

In whole-brain analyses comparing the groups, greater GM volume in Controls than Dyslexics was found in a cluster comprising the left superior temporal gyrus (STG), IFG, insula, as well as in the left limbic (amygdala, hippocampus, subcallosal gyrus) and basal ganglia areas (claustrum, putamen; Fig. 2 and Table 4). The mean GM volume in the observed areas correlated significantly with technical reading score (R=.432, P=.015). Crucially, there was a significant overlap between the aforementioned group difference and the GM structures which

correlated with technical reading skills (Fig. 2 and Table 4). The overlapping area comprised the left STG, insula, and limbic areas (amygdala, hippocampus), and greater GM volume in these areas correlated with higher technical reading score (R=.575, P<.001).

In addition, the control participants had greater WM volume in two clusters in the right MTG and hippocampus as well as in the right precuneus compared with the dyslexic participants (Fig. 2 and Table 4). Again, greater WM volume in these areas correlated significantly with a higher technical reading score (R=.434, P=.015 and R=.406, P=.024, respectively).

Please, insert Fig. 2 around here

Please, insert Table 4 around here

4. **Discussion**

There is an obvious need to understand neural underpinnings of DD, which is highly prevalent and can have devastating effects on the individual affected, yet, no clear consensus has so far been reached (e.g., Ramus et al., 2018, for a review). Our study was set out at illuminating the neuroanatomical basis of DD using a whole-brain volumetric analysis and a thorough reading and neuropsychological test battery. Our main finding was a decreased volume of GM in participants with DD, comprising left frontotemporal and limbic regions as well as the left basal ganglia, a cluster in which greater GM volume was associated with better technical reading abilities across the whole sample. The overlap of areas correlating with reading skills with those having a reduced volume in participants with DD provides a firm basis to interpret that these regions represent the neural origins of dyslexia. These include areas (left STG and IFG, insula) that have previously been linked with the reading network (Kujala et al., 2007) and functional and anatomical abnormalities in dyslexia (Richlan et al., 2009; 2013). Moreover, our study

unravels subcortical structures, the involvement of which in reading and dyslexia have previously been scarcely studied. Also for these areas, our study found associations both with volumetric reductions in participants with DD and reading skills, completing the picture on the neural basis of dyslexia. Moreover, whereas lower total brain volume has so far been the most systematic finding in dyslexia (Ramus et al., 2018, for a review), the total brain volume of our dyslexic sample did not differ from that of our controls. This crucially suggests that dyslexia does not merely result from an overall lower brain volume but from changes in specific brain regions.

4.1 Associations between anatomy and reading-related skills

As could be expected, better performance in technical reading was significantly correlated with neural structures comprising both hemispheres, since a wide range of functions subserved by multiple brain areas are needed for fluent and accurate reading (e.g., Paulesu et al., 2000; Kujala et al., 2007; Levy et al., 2009; Welcome and Joanisse, 2012; Oberhuber et al., 2013). The GM volume findings included the left temporal (STG, MTG, fusiform gyrus), limbic (amygdala, hippocampus, parahippocampal gyrus), and insular areas. In addition, higher technical reading scores were associated with a larger WM volume in right frontal areas (IFG and precentral gyrus), basal ganglia (putamen, globus pallidus), insula, pons, as well as parahippocampal gyrus bilaterally and left cerebellum, closely resembling CPC pathways which have been implicated in language (for a review, see Vias and Dick, 2017). Overall, these results are compatible with a large body of previous research associating reading skills and subskills with brain structures in frontal, temporal, cerebellar, and subcortical areas (Paulesu et al., 2000; Kujala et al., 2007; Levy et al., 2009; Welcome and Joanisse, 2012; Oberhuber et al., 2013; Stoodley and Stein, 2013).

Higher working memory scores were associated with increased WM volume in the brainstem and bilaterally in the cerebellum. This is consistent with a previously found association between working memory load and the amplitude of brainstem responses (Sörqvist et al., 2012), indicating the involvement of brainstem in working memory functions. Brainstem also regulates vigilance (Iovino et al., 2019). Therefore, it could be speculated that these associations are related to attention, which is tightly involved in working memory functions requiring "attentional spotlight" to items that are actively consciously processed (e.g., Rhodes and Cowan, 2018). The association between the cerebellar WM volume and working memory is in accordance with currently known cerebellar functions. Cerebellum is involved in regulating the direction of attention, detecting errors, timing and sequencing, as well as in associative learning, all vitally involving working memory (Stoodley and Stein, 2013, for a review). This is also compatible with the rich cerebellar interconnections with the prefrontal cortex and other association cortices (Stoodley and Stein, 2013), which belong to the neural network responsible for working memory functions (Knight et al., 1999).

We found no significant correlations between phonological scores and neuroanatomical findings. A potential reason for this might be that only relatively small brain areas, suggested to be restricted to the left temporal and angular gyri (Glezer et al., 2016) process phonology and that the present analyses controlling for various nuisance variables impede small effects to become significant. Moreover, while both groups had more than 20 subjects, our overall sample size remained moderate, which in turn decreases power to observe small effects in the data. Furthermore, using our phonological composite score in the correlation analysis might not be optimal, since the tests included tap also into other functions besides pure phonological processing. Another possible explanation is that phonological deficits might primarily arise from subtle anatomical and functional changes in pathways interconnecting posterior and

anterior superior temporal regions (Richardson et al., 2011) rendering the overall methodology (i.e. VBM) disadvantageous here.

4.2 Neuroanatomical group differences

We found reduced GM volume in dyslexic participants in left-hemispheric regions of STG, IFG, insula, limbic system, and basal ganglia, and WM volume in the right temporal, hippocampal and parietal areas. Importantly, the greater GM and WM volumes correlated with better technical reading skills, that is, reading accuracy and speed, directly linking the same brain areas to the core reading skills and reduced neural volumes in DD, which underlines the robustness and reliability of our results. However, interestingly, even though the most robust finding in previous studies has been a reduced total brain volume in DD (see Ramus et al., 2018, for a meta-analysis), we found no group differences in the brain, GM, or WM volumes. Thus, overall volumetric differences do not explain the deficits in reading and related skills in the current sample of dyslexics. This lack of group differences in gross brain volumetric measures is particularly interesting since it has been speculated that reduced brain volume in DD could either be associated with the etiology of DD or a consequence of this disorder (Ramus et al., 2018). However, contradicting results have been published (Frye et al., 2010) and the finding could depend on the population studied (adults vs. children). Our data showing no group differences in a range of volumetric brain measures (TIV, total brain volume, GM volume, WM volume or cerebrospinal fluid volume) suggest that the occurrence of DD may not (only) rely on brain volume reduction as a predisposing factor or as a de rigueur developmental consequence.

Our group and correlational GM volume results in STG, IFG, and insula are consistent with earlier neuroanatomical findings. For example, according to the meta-analysis of Richlan et al.

(2013) the most consistent GM reductions in DD have been found in superior temporal areas and according to the meta-analysis of Ramus et al. (2018) in left perisylvian and OT regions. Furthermore, a large number of studies proposed that these areas belong to a network vital for reading (Kujala et al., 2007; Paulesu et al., 2000; Kujala et al., 2007; Levy et al., 2009; Welcome and Joanisse, 2012; Oberhuber et al., 2013). Our results are also compatible with functional imaging studies on DD, which have revealed hypoactivations in superior, middle, and inferior temporal areas as well as IFG in the left hemisphere (Richlan et al., 2009, for a meta-analysis). Next, we will inspect our findings on brain structures with lower volume in DD and association with technical reading skills in the light of the currently known functions of these areas.

Superior temporal areas were consistently found to be active during reading (Sandak et al., 2004; Richlan, 2014), and proposed to reflect semantic (Helenius et al., 1998; Halgren et al., 2002) and phonological analysis (Jobard et al., 2003). A restricted lesion to left STG was reported to result in pure word deafness, with the patient being able to read, write, and perceive nonspeech auditory stimuli but not to correctly process speech input (Maffei et al., 2017). The reduced GM in the STG of our dyslexic participants might, therefore, reflect a speech-specific deficit, consistent with one of the leading theories on DD according to which reading impairments in DD are largely based on poor speech sound representations (Peterson and Pennington, 2012; see, however, Ramus, 2014). This result is highly compatible with a meta-analysis based on which it was proposed that the phonological processing deficit is an endophenotype of DD (Snowling and Melby-Lervåg, 2016).

Activations of **left IFG** have been reported for words and legal pseudowords (pseudowords not violating the rules of the language) but not for consonant strings (Wilson et al., 2005; Cornelissen et al., 2009) or faces (Cornelissen et al., 2009). Its subregion BA 44 was found to be activated by both words and pseudowords, whereas subregion 45 was only activated by words (during a lexical decision task; Heim et al., 2005). These areas were also found to be

involved in rapid learning of novel word-forms (Kimppa et al., 2015; 2018), an effect not found in dyslexic children (Kimppa et al., 2018). Furthermore, it was proposed that left IFG participates in nonlexical phonological grapheme-phoneme conversion during reading (Heim et al., 2005). Overall, these results, as well as a meta-analysis (Bookheimer 2002), suggest that left IFG regions are involved in word and phonological speech processing. The reduced left IFG GM in our dyslexic participants might, therefore, reflect their observed problems of word-form processing and learning (Kimppa et al., 2018), as well as deficits in phonological processing (e.g., Snowling and Melby-Lervåg, 2016) and grapheme-phoneme conversion (Snowling, 1980).

Whereas the involvement of cortical areas in reading and reading impairment has been extensively studied, less attention has been paid to **subcortical areas** so far (see Krishnan et al., 2016, for a review). Our study revealed a reduced GM volume in the dyslexic sample in limbic (hippocampus and amygdala) and basal ganglia (claustrum and putamen) areas. Similar findings were obtained in the left hemisphere of dyslexic males by Casanova et al. (2005), reporting anomalies in amygdala, hippocampus, putamen, and globus pallidus in their volumetric analysis. Furthermore, in dyslexic children, a successful reading intervention was found to result in increased GM volume in several brain areas including hippocampus (Krafnick et al., 2011). Hippocampus is known to have a central role in memory functions, particularly in memory consolidation (see Buzsáki and Moser, 2013, for a review). A reduced GM in the hippocampus of the dyslexic participants could be associated with their poor ability to "tune in" or form memory representations of novel repetitive stimuli (see Ahissar, 2007, for a review; see also Kimppa et al., 2018). This was suggested to influence the efficacy of short-term memory and underlie a wide range of difficulties associated with DD (Ahissar, 2007).

Amygdala, besides having a central role in processing fear-eliciting stimuli (Markowitsch, 1998) was also suggested to be involved in memory and reward networks and to process

valence, salience, and stimulus relevance (Sander et al., 2003; Janak and Tye, 2015, for reviews), the left amygdala having a higher affinity to language than the right one (Markowitsch, 1998). Processing of relevance and salience, in turn, are strongly linked with attention functions, which are known to be dysfunctional in at least some subgroups of dyslexic individuals (Hari et al., 2001; see Krause, 2017, for a review). Despite our participants having been screened for ADHD with a questionnaire, it is possible that they had some attentional difficulties that do not lead to a suspicion of ADHD.

The putamen has been associated with the initiation of movements (e.g., Tricomi et al., 2009). However, it was also found to be activated more by reading words and pseudowords than by naming pictures and colours (Oberhuber et al., 2013), the effect being stronger in the left than right putamen, suggesting that it belongs to the reading network. The left putamen was found to predominantly coactivate with left-hemispheric regions that have a direct association with language processes (see Vinas-Guasch and Wu, 2017, for a meta-analysis). Our finding of reduced GM in the left putamen in participants with DD is therefore highly compatible with these results.

The claustrum is a narrow structure located between insula and putamen, the functions of which are not well-known. It is thought to be the most densely connected brain structure, involved in integrating a range of cortical inputs and in segregating attention (Goll et al., 2015). Perhaps this diminished GM volume in claustrum in our dyslexic sample might be related to the observed problems in integrating sensory information (e.g., Widmann et al., 2012) and in regulating attention in DD (see Krause, 2015, for a review).Yet, at this stage these suggestions are highly speculative and need confirmation from further studies.

In the current study, group differences in WM volume were limited to right MTG, hippocampus and precuneus, with dyslexic participants having a smaller volume than controls. MTG

(bilaterally) was suggested to be involved in language comprehension (Binder, 2017), and overactivation in right MTG in dyslexic individuals during reading might reflect compensatory functions (meta-analysis of Richlan et al., 2009). Precuneus, in turn, is involved in a wide range of vastly integrated tasks, including episodic memory retrieval and visuo-spatial imagery (Cavanna and Trimble, 2006). Hippocampus, as already discussed, has a central role in memory functions (Buzuki and Moser, 2013). Also some previous studies have shown reduced right-hemispheric WM volumes in DD (e.g., in inferior longitudinal fasciculus, Lu et al., 2016, Banfi et al., 2019) as well as absent rightward asymmetry of the inferior fronto-occipital fasciculus in a subpopulation of DD (Banfi et al., 2019). It could be speculated that the diminished right-hemispheric WM volume of our adults with DD might reflect inefficient compensatory mechanisms, since these participants still had a persistent dyslexia in the adult age.

While our study included 23 dyslexic and 22 control participants, which exceed the minimum group sizes [N (>20)] suggested for neuroanatomical studies on DD (Ramus et al., 2018), even larger sample sizes are needed in the future in order to uncover even finer details of neural deficits associated with DD. Additional limitations of this study are related to the formation of neuropsychological composite scores. The single tests included in the scores could reflect different processes within the composite scores. Although we were not able to conduct a factor analysis for the variables of the current study, the composite variables based on previous theoretical and factor-analytic studies proved to have acceptable internal consistency. Another important limitation is that the two groups were assigned based on subtests included in the technical reading composite score, in addition to one more text reading subtest (section 2.1.). Therefore, the grey-matter group differences and grey-matter volume associations with technical reading should be expected to indicate similar results. The correlations can, in addition to a categorical division of groups, reveal the variance of reading skills within the groups, as well as the direction of the association on a linear scale of reading skills.

4.3 Conclusions

The current study evaluated the neuroanatomical basis of DD using rigorous neuropsychological testing and multiple VBM analyses refined to curtail the common limitations. We found reduced GM volumes in adults with DD in left STG and IFG, which is compatible with proposed core nodes of reading (Kujala et al., 2007) and findings in meta-analyses on GM volumes in DD (e.g., Richlan et al., 2013; Ramus et al., 2018). Furthermore, GM volume reductions were found in our DD sample in subcortical structures, which have so far scarcely been studied, including left limbic and basal ganglia areas. WM reductions, in turn, included right temporal and hippocampal structures, as well as right precuneus. Importantly, these brain areas were also correlated with reading accuracy and speed in the whole sample, sharing significant overlap between the two findings, suggesting that these results illuminate the core dysfunctional neural reading network in DD. Next, it would be important to determine which of these volumetric changes in DD underlie the reading deficit and which ones have resulted from, for example, reduced exposure to print. Moreover, as multiple genetic and environmental risks may lead to reading deficits (e.g., Peterson and Pennington, 2015, for a review), a delineation of subgroups of distinct reading deficit profiles from a larger sample would increase our understanding of DD. This, in turn, is vital for developing interventions that are applicable to individuals with various reading deficit profiles.

Funding

This study was financially supported by the Academy of Finland (grants 276414 and 316970), Jane and Aatos Erkko Foundation, and Kela.

Competing interests

The authors report no competing interests.

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Table 1. Neuropsychological tests and composites (bold).

Neuropsychological composites (bold) and individual tests	Median (IQR)		p_{corr}	signif. level
	Dyslexic (*n* = 23)	**Control (*n* = 22)**		
Phonological processing [z]	-0.2 (1.2)	0.4 (0.4)	<.000	***
Pig Latin (accuracy)	9.0 (7.0)	15.0 (1.0)	<.000	***
Nonword span length (accuracy)	12.0 (3.0)	13.0 (4.0)	.083	ns
Rapid Alternate Stimulus naming (RAS) (speed of second trial)	30.0 (10.7)	24.0 (6.4)	<.000	***
Reading, technical [z]	-0.3 (0.9)	0.6 (0.2)	<.000	***
word list reading (accuracy)	30.0 (1.0)	30.0 (0.0)	.005	**
word list reading (speed)	31.0 (11.4)	19.3 (2.9)	<.000	***
pseudoword list reading (accuracy)	21.0 (8.5)	28.5 (3.5)	<.000	***
pseudoword list reading (speed)	72.9 (32.6)	40.1 (7.7)	<.000	***
text reading (accuracy) #	98.2 (1.1)	99.4 (0.8)	<.000	***
text reading (speed) #	305.0 (67.0)	449.0 (62.8)	<.000	***
Full Intelligence Quotient	104.5 (17.3)	118.0 (11.7)	<.000	***
Verbal IQ [Wechsler Adult Intelligent Scale (WAIS)-III Similarities and Vocabulary]	103.0 (20.0)	115.0 (10.0)	<.000	***
Performance IQ (WAIS-III Block design and Matrix reasoning)	113.0 (11.0)	120.5 (11.6)	.004	**
Working memory functions	19.0 (7.5)	24.0 (5.8)	.007	**
WMS-III Number series	10.0 (3.5)	13.0 (3.8)	<.000	***
WMS-III Visual Series	9.0 (5.0)	10.5 (3.0)	.193	ns

Notes. Group sizes (n) and median values of all variables in the Dyslexic and Control groups with interquartile range (IQR) in parentheses. Group differences were tested with Wilcoxon sign-rank test, and significance levels of FDR-corrected *p*-values are indicated by asterisks. ns – non-significant. #-Not included in the technical reading composite score.

Table 2. Demographic and morphological data

Group sizes (n) and mean values of background variables in the Dyslexic and Control groups with standard deviation in parentheses. P-values show Chi Squared (χ^2), and independent-samples t-test (t) statistics for group comparisons.

	Dyslexic (*n* = 23)	**Control (*n* = 22)**	***P* value**
Demographic			
Gender (male/female)	11/12	10/12	1.000 (χ^2)
Age (years)	31.3 (8.6)	29.8 (5.9)	.530 (*t*)
Education (years)	15.7 (5.2)	16.1 (4.4)	.817 (*t*)
Musical education (years)	3.0 (7.8)	3.7 (5.5)	.730 (*t*)
Morphological			
Grey matter volume (litres)	0.8 (0.1)	0.8 (0.1)	.705 (*t*)
White matter volume (litres)	0.5 (0.1)	0.5 (0.1)	.680 (*t*)
Cerebrospinal fluid volume (litres)	0.5 (0.1)	0.5 (0.2)	.817 (*t*)
Total intracranial volume (litres)	1.8 (0.3)	1.8 (0.3)	.934 (*t*)
Total brain volume (litres)	1.3 (0.1)	1.3 (0.1)	.666 (*t*)

Table 3. Focal grey and white matter volume associations with the neuropsychological composite scores.

Contrast	GMV/WMV	Area name	Coordinates	Cluster size	t-value	Correlation
Technical reading	**GMV**	Left Superior Temporal Gyrus (BA 38)	-32 5 -21	2846	4.94**	TR: R=.634, P<.001
		Left Middle Temporal Gyrus (BA 21)	-48 7 -18			
		Left Fusiform Gyrus (BA 36)	-27 -5 -41			
		Left Insula (BA 13)	-36 10 -14			
		Left Amygdala	-25 -2 -21			
		Left Parahippocampal Gyrus (BA 34)	-16 -3 -20			
		Left Hippocampus	-16 -7 -14			
Technical reading	**WMV**	Right Putamen	29 -8 10	15095	5.24**	TR: R=.606, P<.001
		Right Insula	33 -14 9			
		Right Globus Pallidus	26 -15 -8			
		Right Inferior Frontal Gyrus	46 9 11			
		Right Precentral Gyrus	50 -9 24			
		Left Parahippocampal Gyrus	-18 -19 -14			
		Right Parahippocampal Gyrus	25 -19 -9			
		Pons	-14 -34 -29			
		Left Cerebellum	-17 -45 -33			
Working memory	**WMV**	Brainstem	2 -31 -31	9857	4.69**	WM: R=.518, P=.001
		Left Cerebellum	-16 -42 -31			
		Right Cerebellum	26 -43 -31			

*p < 0.05 FWE-corrected at the cluster level

**p < 0.005 FWE-corrected at the cluster level

All results are thresholded at a whole-brain uncorrected p < 0.005 threshold at the voxel level with a minimal cluster size set to 100 voxels.

Correlations are partial correlations with 2-tailed p-value controlling for age, sex, TIV and FIQ.

BA, Brodmann area, GMV = grey matter volume, TR = Technical reading score, WM = Working memory score, WMV = white matter volume

Table 4. Grey and white matter volume differences between the dyslexic and control groups.

Contrast	GMV/WMV	Area name	Coordinates	Cluster size	t-value	Correlation
Controls > Dyslexics	**GMV**	Left Hippocampus	-20 -8 -12	4866	6.09**	TR: R=.432, P=.015
		Left Amygdala	-29 -3 -22			
		Left Claustrum	-33 1 -1			
		Left Insula (BA 13)	-36 13 -10			
		Left Putamen	-32 0 -4			
		Left Globus Pallidus	-17 -8 -5			
		Left Subcallosal Gyrus (BA 34)	-15 5 -15			
		Left Superior Temporal Gyrus (BA 34, 38)	-40 9 -25			
		Left Inferior Frontal Gyrus (BA 44)	-51 12 4			
Controls > Dyslexics	**WMV**	Right Hippocampus	38 -10 -16	2245	4.53*	TR: R=.434, P=.015
		Right Middle Temporal Gyrus	61 -33 -7			
		Right Precuneus	15 -56 40	1298	4.71*	TR: R=.406, P=.024
Overlap of technical reading (one sample and t-test)	**GMV**	Left Insula (BA 13)	-33 0 -13	769		TR: R=.575, P<.001
		Left Superior Temporal Gyrus (BA 38)	-32 4 -18			
		Left Amygdala	-20 -6 -13			
		Left Hippocampus	-19 -9 -13			

*p < 0.05 FWE-corrected at the cluster level

**p < 0.005 FWE-corrected at the cluster level

All results are thresholded at a whole-brain uncorrected p < 0.005 threshold at the voxel level with a minimal cluster size set to 100 voxels.

Correlations are partial correlations with 2-tailed p-value controlling for age, sex, TIV and FIQ.

BA, Brodmann area, GMV = grey matter volume, TR = Technical reading score, WMV = white matter volume

Figures

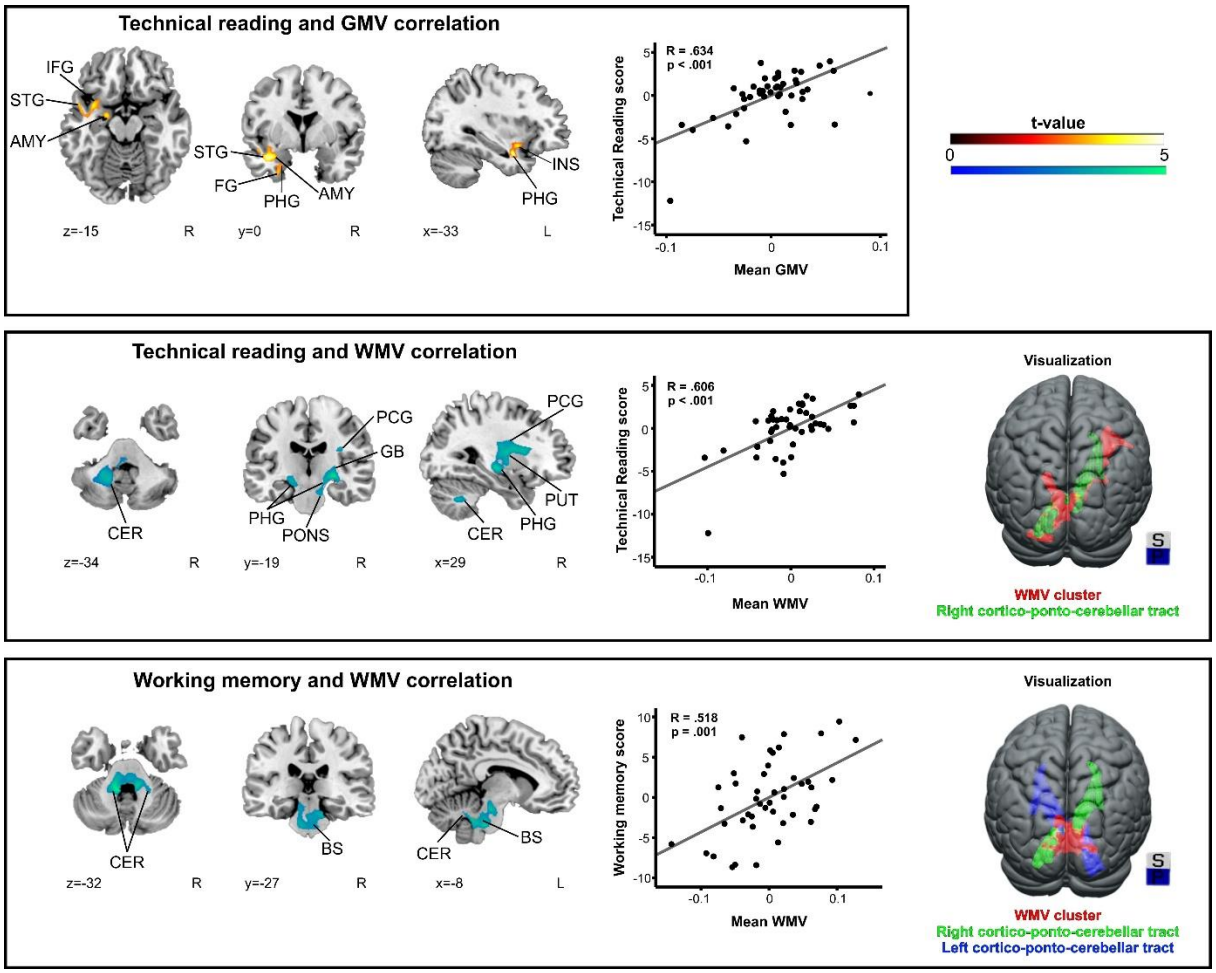

Figure 1.

Grey and white matter volume associations with reading-related skills (see also Table 3). Top: Grey matter volume and technical reading score; Middle: White matter volume and technical reading score; Bottom: White matter volume and working memory score. N = 45. Neurological convention is used with MNI coordinates at the bottom left of each slice. All statistical maps are thresholded at a cluster-level FWE-corrected $p < 0.05$ threshold and corrected for nonstationarity. Grey and white matter volume correlations to reading-related skills are shown with scatter plots. For visualization purposes, a white matter atlas (https://www.natbrainlab.co.uk/atlas-maps) was used to present the white matter volume clusters. AMY = amygdala, BS = brainstem, CER = cerebellum, FG = fusiform gyrus, GB =

globus pallidus, GMV = grey matter volume, IFG = inferior frontal gyrus, L = left, P = posterior, PCG = precentral gyrus, PHG = parahippocampal gyrus, R = right, S = superior, STG = superior temporal gyrus, WMV = white matter volume.

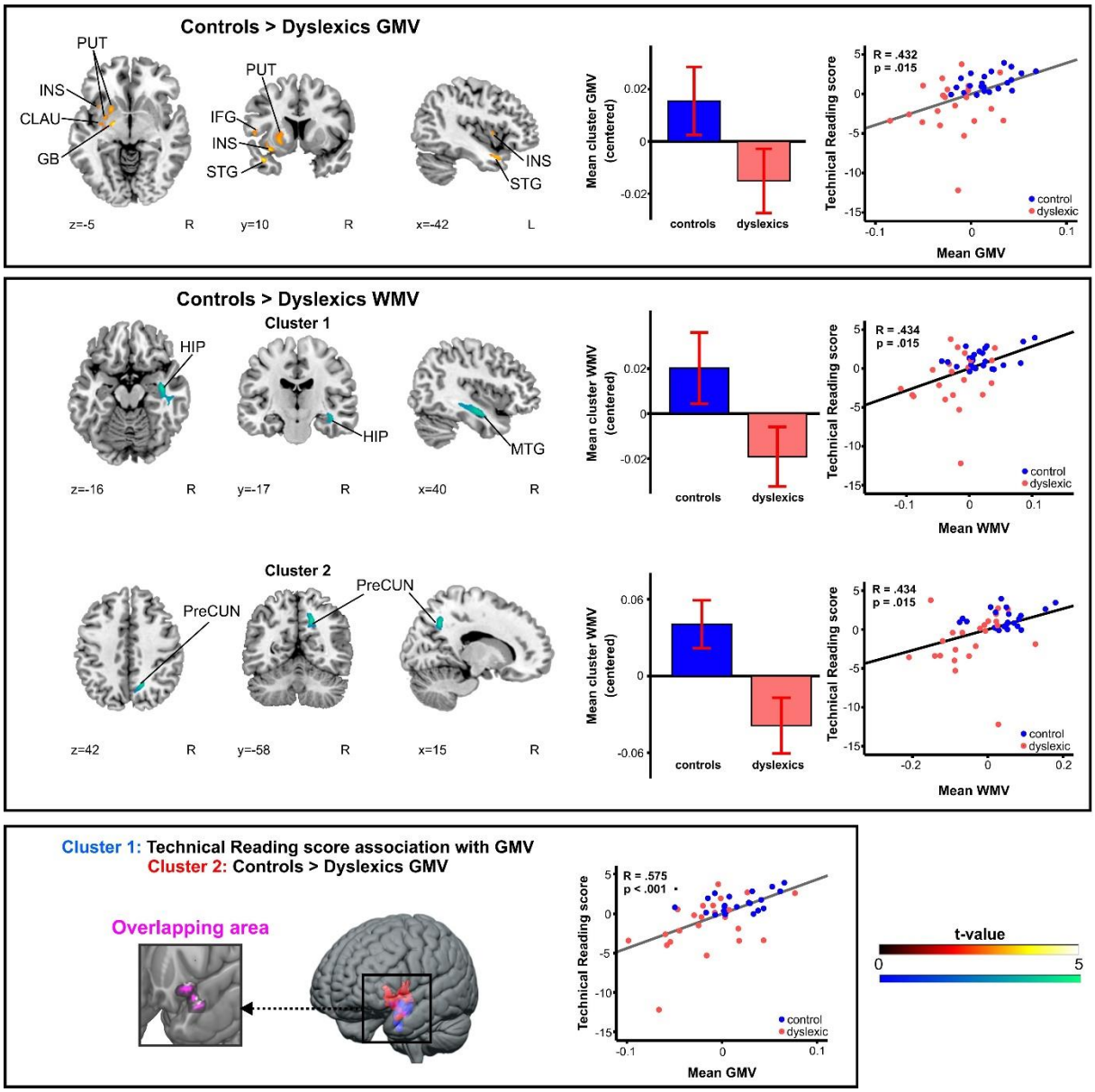

Figure 2.

Grey and white matter volume group differences (see also Table 4). Top: Controls > Dyslexics, grey matter volume; Middle: Controls > Dyslexics, white matter volume; Bottom: Overlap image (purple) of Controls > Dyslexics, grey matter volume (red) and grey matter volume and technical reading score correlation analysis (blue). N = 45. Neurological convention is used with MNI coordinates at the bottom left of each slice. All statistical maps are thresholded at a cluster-level FWE-corrected $p < 0.05$ threshold and corrected for nonstationarity. Grey and white matter volume correlations to reading-related skills are shown with scatter plots. Bar plots

for mean GMV in significant clusters (Table 4) are shown: bar = mean (centered), error-bar = standard error of mean. CLAU = claustrum, GB = globus pallidus, GMV = grey matter volume, HIP = hippocampus, IFG = inferior frontal gyrus, INS = insula, L = left, MTG = middle temporal gyrus, PUT = putamen, PreCUN = precuneus, R = right, STG = superior temporal gyrus, WMV = white matter volume.